RESEARCH ARTICLE

REVISED Potential predictors of adoption of the Tobacco Heating System by U.S. adult smokers: An actual use study [version 2; peer review: 1 approved, 2 approved with reservations]

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Abstract

Background: This was a pre-market, observational, actual use study with the Tobacco Heating System (THS), a candidate modified risk tobacco product. The main goal of the study was to describe THS adoption within current adult daily smokers by replicating the usage of THS in real-world conditions with participants being able to consume cigarettes, THS, and any other nicotine-containing products (e.g., e-cigarettes, cigars, etc.) *ad libitum*.
Methods: This study assessed self-reported stick-by-stick consumption of THS compared with the use of commercial cigarettes over six weeks. The aim of the analysis was to identify potential predictors for adoption of THS using stepwise logistic regression analysis.
Results: By the end of the observational period (in Week 6), 14.6% of participants (n=965) had adopted THS meaning that THS formed 70% or more of their total tobacco consumption. The main predictors of adoption were the liking of the smell, taste, aftertaste, and ease of use of THS. The proportion of adoption was higher in participants aged 44 years and older and in Hispanic or Latino adult smokers. Additionally, adoption of THS was more likely in participants who had never attempted to quit smoking and in participants who smoked up to 10 cigarettes per day. Finally, the adoption of THS was higher in participants who consumed both regular and menthol THS compared with those who consumed only one THS variant.
Conclusions: The findings suggest that the introduction of THS in the U.S. has the potential to result in adoption by current adult smokers who would otherwise continue to smoke cigarettes, and that the adoption of THS is unlikely to result in an increase of tobacco consumption. Post-marketing studies will provide further insights on

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THS adoption and THS use patterns to allow assessment of the impact of the THS at the individual and the overall population level.

Keywords

Harm Reduction, Heat-Not-Burn, Modified Risk Tobacco Product, Actual Use, Product Adoption

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REVISED   **Amendments from Version 1**

Compared to the previous version, the Abstract has been slightly edited to further improve its structure, with no alteration to the message presented. The Introduction was edited to present how other regulatory authorities are considering different types of products, including e-cigarettes, and to provide examples of the MRTPs available in the U.S. (including MRTP applications accepted for review). We also updated in the Introduction the status of the PMI MRTP Applications for *IQOS*. The version of the product provided for the study is now indicated in the Methods. The Discussion section has been reworked to further reflect on the interpretation of the study results together with limitations when it comes to potential inference. The text of the paper has also been modified to improve the English in some places.

Any further responses from the reviewers can be found at the end of the article

Abbreviations

AIC: Akaike Information Criterion; CDC: U.S. Centers for Disease Control and Prevention; CRF: case report form; FDA: U.S. Food and Drug Administration; MRTP: modified risk tobacco product; THS: tobacco heating system

Introduction

Cigarette smoking causes pulmonary, cardiovascular, and other serious diseases and is responsible for the largest number of preventable deaths in the United States (U.S.)[1,2]. It is widely known that the best way to avoid these risks is to never start smoking. For smokers, the best way to reduce the risks and adverse health consequences of smoking is to quit[3]. However, as smoking is addictive, smoking cessation has proven difficult to achieve. Despite a decline in the smoking prevalence in the U.S. from 21% to 16% over the last decade, an estimated 40 million people in the U.S. smoked cigarettes in 2015, with around 30% of them smoking menthol cigarettes[4].

The U.S. Food and Drug Administration (FDA) and other international health authorities have recognized that in order to more rapidly reduce the burden of death and disease from tobacco use, current tobacco control measures should be enriched and complemented by tobacco harm reduction strategies[1,5,6]. Tobacco harm reduction strategies aim to provide smokers who do not want to stop nicotine use with alternative, noncombustible tobacco and nicotine-containing products or nicotine delivery systems that eliminate exposure to smoked tobacco and thus substantially reduce harm compared with smoking combustible products[7–14].

In the U.S., this has given rise to a regulatory framework for manufacturers to market modified risk tobacco products (MRTP), defined as "any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products"[15].

MRTPs aim to avoid the high level of risks of chronic disease, morbidity, and mortality caused by smoking cigarettes on their users, and their risk profile is an essential factor in estimating the public health effects of these products[16]. Examples of MRTPs may include tobacco and/or nicotine-containing products such as e-cigarettes, smokeless tobacco, and heated tobacco products. Various authorities (Public Health England, 2018; Royal College of Physicians, 2016; U.S. Department of Health and Human Services, 2014) have concluded that e-cigarettes for example are likely to be substantially safer than cigarettes. Other products (i.e. heated tobacco products) heat tobacco rather than burning it, thus producing far lower quantities of harmful and potentially harmful constituents (HPHC) than are found in cigarette smoke[13]. While it has been acknowledged that more research on the relative risk of heated tobacco products compared with that of combustible tobacco is needed, the available evidence suggests that heated tobacco products may be considerably less harmful than cigarettes[17,18]. Currently, the most widely available heated tobacco product is the Tobacco Heating System (THS) developed by Philip Morris International (PMI), sold under the *IQOS*[TM] brand name. *IQOS* was launched in 2014 in Italy and Japan. As of March 31, 2021, *IQOS* was available in 66 countries[19]. In July 2020, the FDA authorized the claim 'AVAILABLE EVIDENCE TO DATE: The *IQOS* system heats tobacco but does not burn it. This significantly reduces the production of harmful and potentially harmful chemicals. Scientific studies have shown that switching completely from conventional cigarettes to the *IQOS* system significantly reduces your body's exposure to harmful or potentially harmful chemicals.'[20]. Other MRTP applications have also been accepted for review, made public, and in some cases authorized by the FDA (i.e. General and Camel snus products, Copenhagen moist snuff product, and a very low nicotine cigarette)[21–24].

THS is made up of three distinct components:[25] (1) a tobacco stick, specifically designed for use at low temperatures and containing specially processed crimped tobacco, (2) a holder for the THS Tobacco Stick that electronically heats the tobacco and controls the temperature, and (3) a charger for recharging the holder after each use. THS uses a precisely controlled heating system into which the THS Tobacco Stick is inserted to generate an aerosol without combusting tobacco. The device heats tobacco to significantly lower temperatures (no more than 350°C) than cigarettes, thereby significantly reducing or eliminating HPHCs from the inhaled aerosol compared with cigarette smoke. The substantial reduction in toxic emission and subsequent body exposure have been established by the THS manufacturer (PMI) and competitors[25–40]. Though a few studies have brought contradictory evidence[41,42], the weight of evidence produced by independent studies, including FDA laboratory tests, confirms PMI's findings on the substantial reduction of major carcinogens[17,34,43–47]. While prevalence data are still sparse, evidence from Japan, where *IQOS* was first launched, suggests a steady increase in awareness and use of *IQOS* between 2015 and 2017[48,49]. Analysis of predictors of *IQOS* current use (use in the previous 30 days) in 2017 showed that current Japanese smokers with intention to quit had higher odds to use *IQOS* than that of those with no intention to quit (13.3 vs. 6.7), while women aged 60 years or more showed

significantly lower odds than reference categories[49]. Ever-use of e-cigarettes was associated with greater odds of using *IQOS*. These findings suggest that the large majority of *IQOS* users in Japan switched from cigarettes to *IQOS* and that there is minimal uptake from nonsmokers. However, they provide limited information on how *IQOS* would impact public health in countries other than Japan[48,49].

More specifically, in the context of an MRTP application, the FDA recommends assessment of the public health impact of candidate MRTPs under close to real-world conditions to understand how U.S. adult consumers actually use the product[50], thus requiring actual use evidence for a product which is not yet commercialized in the U.S. The U.S. Institute of Medicine recommended studies that provide real-world evidence, including *ad libitum* use of MRTPs alone and in combination with cigarettes[7]. Although real-world evidence is generally gathered from observational studies in a post-market setting, as with over-the-counter drugs, where consumers are provided with the product together with labeled directions for use[51–53], most of the actual use data that have been collected on potential MRTPs have been done in an artificial setting, and the MRTP is provided for free, as opposed to what happens for other commercialized tobacco products in real-life conditions[54–56].

The present study reports the findings of a pre-market actual use study performed in the context of *IQOS* MRTP application to the FDA[57]. The goal of the study was to measure THS use patterns in U.S. adult daily cigarette smokers and to assess THS product acceptance.

To mimic real-life situations as closely as possible, adult daily smokers had access to THS regular and menthol flavor products and were free to consume cigarettes, THS, and any other nicotine-containing products *ad libitum*.

The present analysis aims at identifying the potential predictors (i.e., socio-demographics, smoking habits, sensory assessment,

and ease of use) of THS adoption in adult cigarette smokers. The effect of THS product flavor (i.e., regular or menthol) was also investigated.

Methods
Study design
The actual use observational study consisted of one-week baseline period, a six-week observational period, and a one-week close-out period (see Figure 1)[57]. During the baseline period, participants recorded their regular cigarette consumption. During the subsequent observational period, participants recorded their consumption of both cigarettes and THS. Throughout the entire observational period, all participants were free to consume cigarettes, THS, and any other nicotine-containing products *ad libitum*. The observational period served to assess the development of THS use patterns. A close-out period was implemented for safety surveillance.

Setting
The study was conducted between 21 September 2015 and 7 January 2016 in eight cities located across the U.S. (Asheville, NC; Charlotte, NC; Denver, CO; Detroit, MI; Las Vegas, NV; Miami, FL; Oklahoma City, OK; Tampa, FL). The study locations were chosen to recruit a sufficiently large and diverse number of current U.S. adult daily smokers. In each city, the research and recruitment agency C&C Market Research operated a dedicated booth within a mall, which was used as a study site. All study materials were reviewed and approved on 28 August 2015 by Sterling Institutional Review Board (ID: 5149-001) before actual study implementation. This study was performed in accordance with Good Epidemiological Practice[58].

Participants
Study participants were recruited from the C&C Market Research databases. C&C's databases consist of approximately 400,000 individuals nationwide who are recruited to join the site database via mall intercept, word of mouth, or by visiting
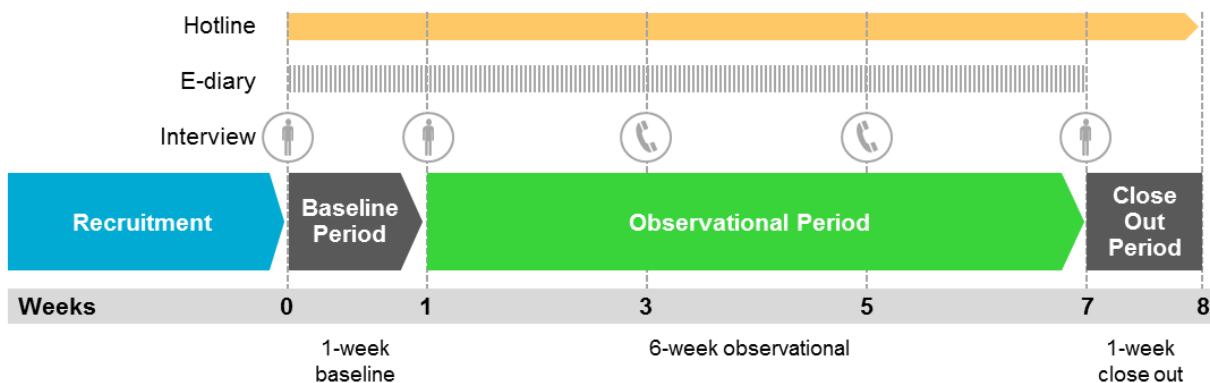
Figure 1. Scheme of study events. * During the baseline and the observational periods, participants recorded their stick-by-stick consumption of cigarettes and/or THS into an electronic diary (e-diary). Participants were able to call the toll-free telephone hotline to raise queries related to the study, resolve issues related to the e-diary or THS, and report product quality complaints and adverse health events associated with the use of THS.

the C&C Market Research website. The sampling was designed using quotas in terms of sex (male (56%); female (44%)), age (18–24 years old (34%); 25–44 years old (34%); 45+ years old (32%)), race (white (70%); black or African American (30%)), and income (low (48%); moderate/high (52%))[1].

Based on information available for each person (e.g., age, gender, smoker/nonsmoker, etc.) within the database, individuals employed by C&C Market Research randomly contacted potential study participants via telephone. No specific method or particular order was utilized for the selection of study participants beyond ensuring that the quotas were met. Individuals who met the following inclusion criteria were eligible for the study: (a) 18 years of age or above according to the minimum legal age), (b) currently living in the U.S., (c) current daily smokers of regular and/or menthol cigarettes with no intention of quitting within the next 30 days, (d) interest in participating in an eight-week study and providing informed consent. The following individuals were excluded from the study: (a) women who, based on self-report, were either pregnant, breastfeeding, or of childbearing potential and not using adequate means of contraception, and (b) individuals who had started smoking within the last 30 days. Eligible individuals were then invited to a study site, where they were rescreened for eligibility based on their ID document for proof of age and were asked their intention to use THS based on their reading of a multipage information brochure on THS (*Extended data*[59]). Only participants with a positive intention (i.e., "somewhat likely", "very likely", "definitely" using a six-point Likert scale ranging from "definitely not" to "definitely") were enrolled in the study.

Sample size calculation was based on a precision-based approach (accuracy in parameter estimation) based on predetermined tightness of the confidence intervals. Given a precision of ± 5% for 95% confidence intervals of prevalence estimates and assuming a proportion of 50% of participants passing a consumption threshold of 100 THS products and 40% attrition, the study aimed to recruit 1,300 participants.

Products
The investigational tobacco product as part of this actual use study was THS Version 2.2 and was provided by PMI. Products available to participants during the observational period had a neutral design with study identification elements to ensure confidentiality of the THS material, given the pre-market nature of the actual use study. U.S. Surgeon General's warnings were present on each THS pack in a rotating fashion.

Data collection and measurements
At enrollment in the study, participants completed an informed consent form and were interviewed in person by trained staff from the C&C Market Research study site in order to provide information on the purpose and goal of the study and instructions on how to use an electronic diary to report tobacco

consumption. Questionnaires were also administered to collect demographic information, such as sex, age, race, ethnicity, education, occupation, and income as well as information on smoking habits, including the average number of cigarettes smoked per day, type of cigarette (menthol, regular), current usage of e-cigarettes, current usage of nicotine replacement therapy products, attempts to quit smoking, and the likelihood as well as the reasons to use THS regularly.

During the one-week baseline period, participants were requested to make an entry into an electronic diary (e-diary) every time they consumed a cigarette. Upon completion of the one-week baseline period, participants returned to the study site to receive THS and choose between THS regular, menthol, or a combination of the two products, according to their taste preference. Participants were provided with a maximum of 100 THS products at the start of the observational period. This supply ensured that all participants had access to THS on the initial days of participation in the observational period. During the remaining study period, participants could request additional THS products. Excessive ordering of additional THS was prevented by fixing an individual maximum number, based on self-reported cigarette consumption assessed at enrollment and then applying an "inflation factor" of three to allow for potential increase of use of THS.

During the six-week observational period, participants were requested to make an entry into the e-diary every time they consumed a THS or a cigarette. If no entries were made until a predefined time point per day, the e-diary sent an acoustic signal and displayed a reminder to record consumption. E-diary data were transferred automatically to a central database each night. In addition, participants were interviewed every two weeks to assess the taste, smell, aftertaste, and ease of use of THS (telephone interviews at Weeks 3 and 5 and personal interview at Week 7). Taste, smell, and aftertaste were assessed using a seven-point Likert scale ranging from one to seven, where one represented "I don't like it at all", and seven represented "I like it very much". Similarly, ease of use was measured using a seven-point Likert scale ranging from one to seven, where one was "not easy to use at all", and seven was "very easy to use".

Participants were able to call the toll-free telephone hotline to raise queries related to the study, resolve issues related to the e-diary or THS, and report product quality complaints and adverse health events associated with the use of THS. At the end of the observational period, participants were asked to return all study materials. During the "close-out" week period participants were not required to record any data, however, for the continued surveillance of potential adverse events (AEs), they were able to call the toll-free telephone hotline to report if they experienced any adverse events with the use of THS during the course of the study.

Study participation was voluntary, and participants were free to withdraw at any time. Compensation in the study was based on participants' level of participation and on compliance

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[1]Low income (annual household ≤ $44,999); moderate/high income (annual household ≥ $45,000).

with the study procedures (maximum of $440) and paid via check at the end of the study.

Variables

The main outcome measure was self-reported consumption of cigarettes and THS during the observational period. This measure was used to derive a variable describing the percentage of *THS use* on a weekly basis by dividing the number of THS products by the number of total tobacco products used (THS products plus cigarettes). In order to facilitate meaningful description and interpretation of THS use patterns and future comparison across various studies[60], this product use variable was then trichotomized into the following predefined usage categories: (1) *THS use* ($\geq$ 70% of total tobacco product used being THS[70–100]% THS), (2) *combined use* (> 30% to < 70% of total tobacco product used being THS]30–70[% THS), and (3) *cigarette use* ($\leq$ 30% of total tobacco product used being THS [0–30]% THS). In addition, "Adoption of THS" at Week 6 was defined as $\geq$ 70% of THS products in a participant's combined consumption of tobacco products during Week 6.

The following variables were evaluated as potential predictors of THS adoption (Table 1):

Demographics. From the demographic collection at enrollment, the following variables were derived: sex, age (18–24 years, 25–44 years, above 44 years), race (white, black or African American/Other), ethnicity (Hispanic or Latino, not Hispanic or Latino), income (low, moderate, high), number of persons (1 person, > 1 person) and children (none, 1 or more children) in household, marital status (no relationship, relationship), occupational status (at work, not at work), educational attainment (low/moderate, high), socio-economic status (low/moderate, high). In addition, study site location (eight cities) was also considered as a potential demographic predictor.

Smoking behavior. From the smoking habits questionnaire at enrollment, the following variables were derived: average number of cigarettes per day (1–10 cigarettes, 11–20 cigarettes, $\geq$ 21 cigarettes), usage of e-cigarettes (yes, no), intention to quit smoking within the next six months (no or don't know, yes), last attempt to quit smoking (some time in the past, never). In addition, the type of THS products ordered through the study observational period was also considered as a predictor of THS adoption (only regular, only menthol, both types).

Product assessment. Taste, smell, and aftertaste assessment collected at the end of the study (Week 7) were aggregated to quantify sensory assessment into four quartiles. Ease of use assessment was aggregated into three categories (not easy to use, quite easy to use, easy to use).

Analysis

The study population for analysis included all participants who (1) fulfilled all eligibility criteria, (2) had at least one documented consumption of a cigarette during the baseline period, and (3) had at least one documented consumption of a THS product during the observational period.

Potential predictors of THS adoption underwent bivariate screening using the Chi-squared test (see Table 1). Predictors with a p-value < 0.2 were subsequently subjected to stepwise logistic regression, with sex, age, and THS product types ordered being forced-in variables. Backward selection was applied to identify the final model, with $p < 0.05$ as the selection threshold to retain variables. The resulting model was compared with the model identified by forward selection using the same variables. In case of a difference between the models, the better model based on the Akaike Information Criterion (AIC) was chosen[61].

Additionally, the process was repeated using two-way interaction terms between THS product types ordered and each independent variable with p-value < 0.2 from the bivariate screening with simple logistic regressions. The two resulting multiple logistic regression models with and without interaction terms were compared using the AIC.

Analysis was conducted using SAS, version 9.4 (SAS Institute Inc. Cary, NC, USA). All analyses were descriptive and exploratory. No imputation of missing data was applied. Percentages were calculated as proportion of each category based on all non-missing values.

Results

Study participants

Out of the database managed by C&C Market Research, 8,858 members were contacted via telephone. Of these, 1,860 refused to continue the telephone conversation, 5,630 did not meet the eligibility criteria, and the remaining 1,368 were invited to the closest study site and rescreened against inclusion/exclusion criteria to verify eligibility. Of the 1,336 participants who were enrolled into the study, 1,106 participants self-reported at least one cigarette during the baseline period and at least one THS product during the observational period. At the end of the observational period (Week 6), 968 participants had reported data in e-diaries. Of these, three participants reported use of zero THS products or cigarettes. Thus, the analysis population consisted of 965 participants.

The proportion of male participants (49%) in the analysis population was very similar to the proportion of female participants (51%). More than 75% of the participants were 25+ years old, about two thirds (68%) were white, and slightly more than half (56%) had a yearly household income below $45,000 (Table 1).

THS product types

Of the analysis population (965 participants), 424 participants (43.9%) ordered only menthol THS products, 365 participants (37.8%) ordered only regular THS products, and 172 participants (17.8%) ordered both types.

Table 1. Demographic characteristics and potential predictors by adoption of THS at the end of the observational period.

		Total[1]	Adoption of THS	No adoption of THS	*p*-value for Chi-square
All participants		965 (100%)	141 (14.6%)	824 (85.4%)	.
Demographics[2]					
Sex	Male	474 (49.1%)	81 (17.1%)	393 (82.9%)	0.0323
	Female	491 (50.9%)	60 (12.2%)	431 (87.8%)	
Age in categories	18 to 24 years	223 (23.1%)	24 (10.8%)	199 (89.2%)	0.1671
	25 to 44 years	363 (37.6%)	59 (16.3%)	304 (83.7%)	
	Above 44 years	379 (39.3%)	58 (15.3%)	321 (84.7%)	
Persons in household in categories	1 person	216 (22.4%)	38 (17.6%)	178 (82.4%)	0.1591
	> 1 person	749 (77.6%)	103 (13.8%)	646 (86.2%)	
Children in household in categories	None	615 (63.9%)	96 (15.6%)	519 (84.4%)	0.2586
	1 or more children	348 (36.1%)	45 (12.9%)	303 (87.1%)	
Marital status	No relationship	729 (75.5%)	114 (15.6%)	615 (84.4%)	0.1126
	Relationship	236 (24.5%)	27 (11.4%)	209 (88.6%)	
Occupational status	At work	597 (61.9%)	87 (14.6%)	510 (85.4%)	0.9520
	Not at work	367 (38.1%)	54 (14.7%)	313 (85.3%)	
Educational attainment	Low and moderate	452 (46.9%)	72 (15.9%)	380 (84.1%)	0.2822
	High	512 (53.1%)	69 (13.5%)	443 (86.5%)	
Income levels	Low	334 (36.1%)	54 (16.2%)	280 (83.8%)	0.2424
	Moderate	413 (44.7%)	62 (15.0%)	351 (85.0%)	
	High	177 (19.2%)	19 (10.7%)	158 (89.3%)	
Socio-economic status	Low and moderate	339 (36.7%)	54 (15.9%)	285 (84.1%)	0.3934
	High	584 (63.3%)	81 (13.9%)	503 (86.1%)	
Race	White	653 (67.8%)	88 (13.5%)	565 (86.5%)	0.1376
	Black or African American/Other	310 (32.2%)	53 (17.1%)	257 (82.9%)	
Ethnicity	Hispanic or Latino	115 (11.9%)	27 (23.5%)	88 (76.5%)	0.0041
	Not Hispanic or Latino	850 (88.1%)	114 (13.4%)	736 (86.6%)	
Study location	Asheville	119 (12.3%)	11 (9.2%)	108 (90.8%)	0.1194
	Charlotte	109 (11.3%)	10 (9.2%)	99 (90.8%)	
	Denver	134 (13.9%)	21 (15.7%)	113 (84.3%)	
	Detroit	121 (12.5%)	14 (11.6%)	107 (88.4%)	
	Las Vegas	121 (12.5%)	22 (18.2%)	99 (81.8%)	
	Miami	124 (12.8%)	25 (20.2%)	99 (79.8%)	
	Oklahoma City	111 (11.5%)	16 (14.4%)	95 (85.6%)	
	Tampa	126 (13.1%)	22 (17.5%)	104 (82.5%)	
Smoking behavior					
Average number of cigarettes per day in categories	1–10 cigarettes	405 (42.0%)	72 (17.8%)	333 (82.2%)	0.0318

		Total[1]	Adoption of THS	No adoption of THS	*p*-value for Chi-square
	11–20 cigarettes	439 (45.5%)	58 (13.2%)	381 (86.8%)	
	≥ 21 cigarettes	121 (12.5%)	11 (9.1%)	110 (90.9%)	
Usage of e-cigarettes	No	913 (94.6%)	129 (14.1%)	784 (85.9%)	0.0756
	Yes	52 (5.4%)	12 (23.1%)	40 (76.9%)	
Intention to quit smoking within the next 6 months	No and don't know	929 (96.3%)	134 (14.4%)	795 (85.6%)	0.4027
	Yes	36 (3.7%)	7 (19.4%)	29 (80.6%)	
Last attempt to quit smoking	Some time in the past	391 (40.5%)	43 (11.0%)	348 (89.0%)	0.0087
	Never	574 (59.5%)	98 (17.1%)	476 (82.9%)	
THS Tobacco Sticks type ordered	Only regular THS Tobacco Sticks	365 (37.8%)	43 (11.8%)	322 (88.2%)	0.0069
	Only menthol THS Tobacco Sticks	424 (43.9%)	59 (13.9%)	365 (86.1%)	
	Both THS Tobacco Sticks types	172 (17.8%)	39 (22.7%)	133 (77.3%)	
	THS Tobacco Sticks consumption type not available	4 (0.4%)	0	4 (100%)	
Product assessment					
Sensory assessments (taste, smell, aftertaste)[3]	First quartile (< 2.0)	225 (24.0%)	13 (5.8%)	212 (94.2%)	< .0001
	Second quartile (2.0 to < 3.5)	288 (30.7%)	27 (9.4%)	261 (90.6%)	
	Third quartile (3.5 to < 5.0)	209 (22.3%)	35 (16.7%)	174 (83.3%)	
	Fourth quartile (≥ 5.0)	215 (22.9%)	63 (29.3%)	152 (70.7%)	
Ease of use[4] assessment	Not easy to use (1,2,3)	301 (32.1%)	18 (6.0%)	283 (94.0%)	< .0001
	Quite easy to use (4,5)	276 (29.5%)	33 (12.0%)	243 (88.0%)	
	Easy to use (6,7)	360 (38.4%)	87 (24.2%)	273 (75.8%)	

[1] n = 965, excluding three participants without any reported Tobacco Stick or cigarette use within Week 6. Only nonmissing data are shown in the table.

[2] Categories recorded in the case report form (CRF) were condensed in order to reduce the number of estimators and balance the number of subjects per category: Persons in household in categories: 1 person, > 1 person

Children in household in categories: None; 1 or more children. Information on children in household was missing for two participants.

Marital status: Relationship (CRF categories: Living with someone / Married), No relationship (CRF categories: Never married / Legally separated / Divorced / Widowed)

Occupational status: At work (CRF category: working now), Not at work (CRF categories: Only temporarily laid off, sick leave or maternity leave / Looking for work, unemployed / Retired /Disabled, permanently or temporarily / Homemaker, keep housing / Student / Other). Information on occupational status was missing for one participant.

Educational attainment: Low (CRF category: less than high school diploma) / moderate (CRF category: high school diploma), High (CRF categories: some university training or university degree). Information on educational attainment was missing for one participant.

Income levels: Low (CRF categories: Less than $30,000), moderate (CRF categories: $30,000 to less than $60,000), High (CRF categories: $60,000 and more). Information on income level was missing for 41 participants.

Socio-economic status is derived as a combination of income levels and educational attainment: Low (low income and low education), Moderate (low income and moderate education, low income and high education, moderate income and low education, and high income and low education), and High (moderate income and moderate education, moderate income and high education, high income and moderate education, and high income and high education). Information on socio-economic status was missing for 42 participants.

Race: White, Black or African American/Other (CRF categories: American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander). Information on race was missing for two participants.

Last attempt to quit smoking: Some time in the past (CRF categories: less than 6 months ago, more than 6 months ago), Never.

[3] The taste, smell, and aftertaste of the product were assessed using a seven-point scale ranging from 1 = "I don't like it at all" to 7 = "I like it very much". For the scale assessments, Cronbach's alpha was calculated as measure of internal consistency among the scales. Because of an alpha of 0.89 (above the threshold value of 0.8), a combined construct of sensory acceptance was calculated using the mean scale assessments over taste, smell, and aftertaste. Four categories were created based on the quartiles of the distribution of these mean scale assessments. Information on sensory assessment was missing for 28 participants.

[4] Ease of use of the product was assessed using a seven-point scale ranging from 1 = "not easy to use at all" to 7 = "very easy to use". Information on ease of use was missing for 28 participants.

Usage patterns of tobacco products

The proportion of participants with *THS use* decreased between Week 1 (19.4%) and Week 6 (14.6%). Usage patterns of THS products were relatively stable in Weeks 4, 5, and 6 of the observational period.

The proportion of participants with *combined use* (> 30% and < 70% THS) decreased from 41.5% at Week 1 to 22.4% at Week 6, while the proportion of participants with *cigarette use* (≤ 30% THS) increased from 39.0% at Week 1 to 62.7% at Week 6.

The number of tobacco products (THS products and cigarettes) consumed per day during the observational period was lower than the number of cigarettes consumed per day during the baseline period across all participant groups at Week 6. The mean (± standard deviation) number of tobacco products decreased from 9.0 ± 5.89 to 8.1 ± 5.37 in participants with *THS use*, from 9.3 ± 6.34 to 8.9 ± 6.21 in participants with *combined use*, and from 10.9 ± 7.69 to 9.9 ± 6.75 in participants with *cigarette use* (Table 2).

Potential predictors of adoption of THS

At the end of the observational period (Week 6), 14.6% of the analysis population had adopted *THS use* (Table 1). The proportion of participants adopting THS was higher in males (17.1% vs. 12.2%), in participants aged more than 25 years (25 to 44 years: 16.3%, above 44 years: 15.3% vs. 18 to 24 years: 10.8%), in one person households (17.6% vs. 13.8%), in participants with no relationship (15.6% vs. 11.4%), in black or African Americans (17.1% vs. 13.5%), and in Hispanic or Latino participants (23.5% vs. 13.4%).

With regard to smoking habits, the proportion of participants adopting THS was higher in participants smoking from one to 10 cigarettes per day (17.8% vs. 11 to 20 cigarettes per day: 13.2% and ≥ 21 cigarettes per day: 9.1%), e-cigarette users (23.1% vs. 14.1%), and in participants who never attempted to quit smoking (17.1% vs. 11.0%). The proportion of participants who adopted THS was higher in those who ordered both THS products (22.7% vs. 13.9% for menthol only vs. 11.8% for regular only).

The proportion of participants adopting THS was higher in participants who liked the taste, smell, and aftertaste of THS (increasing from 5.8% in the first quartile to 29.3% in the fourth quartile for sensory assessment scores) and in participants who found THS easy to use (increasing from 6.0% in participant who found THS not easy to use to 24.2% in participants who found THS easy to use).

Stepwise main effects logistic regression analysis resulted in the same model, max-rescaled R-square of 0.1968 and 76.2% of concordant pairs, regardless of the selection method (i.e., forward or backward). The predictors of adoption of THS at the end of the observational period are summarized in Figure 2.

No influence of sex (OR = 0.71 [95% CI: 0.48–1.06]) was found, but adoption of THS was more likely in participants aged more than 44 years (OR = 2.01 [95% CI: 1.13–3.58]) and in participants who ordered both THS product types (OR = 1.86 [95% CI: 1.10–3.14]).

Sensory assessment and ease of use were the main predictors for THS adoption. The odds of adopting THS were more than four times higher in participants who liked the smell, taste, and aftertaste of THS (≥ 5.0 points on a seven-point scale) (OR = 4.44 [95% CI: 2.26–8.73]). Similarly, the odds to adopt THS were more than three times higher in participants who found THS easy to use (OR = 3.39 [95% CI 1.89–6.07]).

Participants who had never attempted to quit smoking had a higher chance of adopting THS compared with those who attempted to quit at some time in the past (OR = 1.73 [95% CI 1.14–2.63]).

Table 2. Number of THS sticks and/or cigarettes reported per day in different main product use categories[1]

	THS use at Week 6 (n=141)		Combined use at Week 6 (n=217)		Cigarette use at Week 6 (n=607)	
	Mean	SD	Mean	SD	Mean	SD
During baseline period						
Number of cigarettes	9.0	5.89	9.3	6.34	10.9	7.69
During observational period						
Number of tobacco products (THS products and cigarettes)	8.1	5.37	8.9	6.21	9.9	6.75
Number of cigarettes	1.4	1.57	4.8	3.72	8.3	6.32
Number of THS products	6.7	4.82	4.1	3.06	1.7	1.99

[1] Definitions: *THS use*: ≥ 70% of total tobacco product used being THS, (2) *combined use*: > 30% to < 70% of total tobacco product used being THS, and (3) *cigarette use*: ≤ 30% of total tobacco product used being THS.
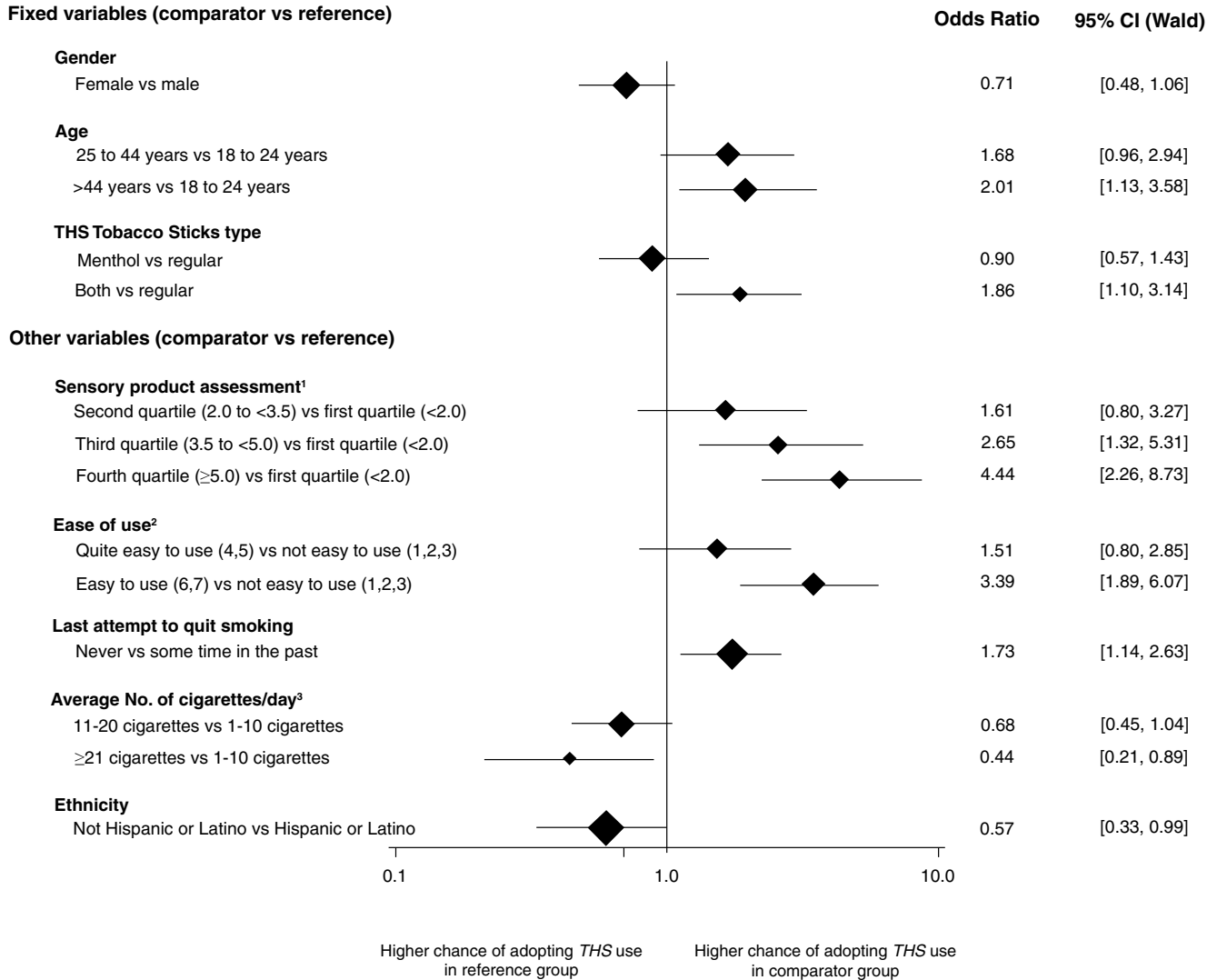
Fixed variables (comparator vs reference)   **Odds Ratio**   **95% CI (Wald)**

	Odds Ratio	95% CI (Wald)
Gender		
Female vs male	0.71	[0.48, 1.06]
Age		
25 to 44 years vs 18 to 24 years	1.68	[0.96, 2.94]
>44 years vs 18 to 24 years	2.01	[1.13, 3.58]
THS Tobacco Sticks type		
Menthol vs regular	0.90	[0.57, 1.43]
Both vs regular	1.86	[1.10, 3.14]
Other variables (comparator vs reference)		
Sensory product assessment[1]		
Second quartile (2.0 to <3.5) vs first quartile (<2.0)	1.61	[0.80, 3.27]
Third quartile (3.5 to <5.0) vs first quartile (<2.0)	2.65	[1.32, 5.31]
Fourth quartile (≥5.0) vs first quartile (<2.0)	4.44	[2.26, 8.73]
Ease of use[2]		
Quite easy to use (4,5) vs not easy to use (1,2,3)	1.51	[0.80, 2.85]
Easy to use (6,7) vs not easy to use (1,2,3)	3.39	[1.89, 6.07]
Last attempt to quit smoking		
Never vs some time in the past	1.73	[1.14, 2.63]
Average No. of cigarettes/day[3]		
11-20 cigarettes vs 1-10 cigarettes	0.68	[0.45, 1.04]
≥21 cigarettes vs 1-10 cigarettes	0.44	[0.21, 0.89]
Ethnicity		
Not Hispanic or Latino vs Hispanic or Latino	0.57	[0.33, 0.99]

0.1   1.0   10.0

Higher chance of adopting *THS* use   Higher chance of adopting *THS* use
in reference group   in comparator group

Figure 2. Predictors of adoption of THS at the end of the observational period. The vertical line shows the value where chances of adopting are equal in both the reference and the comparator group. Horizontal lines show the confidence intervals. The size of the diamonds is proportional to the number of participants in the comparator group. [1] The taste, smell, and aftertaste of the product were assessed using seven-point scales ranging from 1 = "I don't like it at all" to 7 = "I like it very much". For the scale assessments, Cronbach's alpha was calculated as measure of internal consistency among the scales. Because of an alpha of 0.89 (above the threshold value of 0.8), a combined construct of sensory acceptance was calculated using the mean scale assessments over taste, smell, and aftertaste. Four categories were created based on the quartiles of the distribution of these mean scale assessments. [2]Ease of use of the product was assessed using a seven-point scale ranging from 1 = "not easy to use at all" to 7 = "very easy to use". [3]Average number of cigarettes/day at enrollment.

Participants who smoked on average ≥ 21 cigarettes/day had a lower chance of adopting THS compared with those who smoked on average 1–10 cigarettes/day (OR = 0.44 [95% CI 0.21–0.89]), and the same applied for non-Hispanic or Latino participants compared with Hispanic or Latino participants (OR = 0.57 [95% CI 0.33–0.99]) (Figure 2). Interaction terms with the consumed THS product type did not improve the overall model fit.

Discussion

The main goal of this study was to describe THS adoption in a real-world setting and to identify potential predictors for adoption of THS. This actual use study was conducted in U.S. adult daily smokers and included 1,106 participants self-reporting their consumption of cigarettes and/or THS products using an e-diary.

During the observational period, the proportion of participants with *THS use* was stable from Week 4 onwards and by Week 6, almost 15% of the participants had adopted THS, suggesting that THS is a viable alternative to cigarettes for adult smokers. The results do not indicate an increase of overall tobacco consumption over the observational period. Therefore, even though dual use is likely to happen in the first weeks of THS

use, it is unlikely to lead to higher abuse liability and increase exposure to tobacco and nicotine products.

The adoption of THS was higher in participants ordering both THS types compared with participants ordering only regular or only menthol THS, suggesting that the availability of several variants of THS, including menthol, might result in a higher proportion of U.S. adult smokers substituting cigarettes with THS. Similar findings have been reported in studies with e-cigarettes and noncombustible nicotine products[62–65]. Some of these studies also indicated that the use of menthol can facilitate the transition from cigarettes to MRTPs, such as heated tobacco products[62–65]

Participants who liked the smell, taste, and aftertaste of THS and participants who found THS easy to use were more likely to adopt THS, compared with participants who did not like THS smell, taste, and aftertaste or did not find THS easy to use. This finding supports results from previous studies that found that one of the main reasons that people stop using e-cigarettes after trying them is that they do not like the taste[65–68].

Participants smoking 1–10 cigarettes per day were more likely to adopt THS than participants smoking more than 21 cigarettes/ day. A similar outcome has been reported for e-cigarettes, as indicated by the prevalence of regular use of e-cigarettes being higher among adult smokers who smoke a lower number of cigarettes per day[69].

Participants who never attempted to quit smoking in the past were more likely to adopt THS than participants who had previously attempted to quit smoking. Intention to quit smoking within the next six months was not associated with THS adoption suggesting that the availability of THS is unlikely to interfere with intention to quit smoking.

The proportion of THS adoption was higher in participants aged 44 years and older compared with participants aged between 18 and 24 years old. Hispanic or Latino participants had a slightly higher likelihood of adopting THS than non-Hispanic or Latino participants.

Other demographic characteristics, such as sex, household size, educational attainment, income levels, or race, were not associated with THS adoption.

Overall, these findings show that the socio-demographic characteristics of smokers who are more likely to adopt THS tend to differ from what has been recently reported on e-cigarettes, particularly in terms of age, ethnicity, and previous quit attempts[69]. This suggests that THS may be seen as an acceptable substitute for cigarettes to a different category of smokers than those who are currently using e-cigarettes. This is corroborated by the fact that current e-cigarette use was not associated with THS adoption.

Importantly, the study findings highlight the importance of offering alternatives that are close to cigarettes from a sensory experience for the adoption of MRTPs, such as heated tobacco

products[65–68], with product liking and ease of use being more important predictors for adoption of THS than socio-demographic characteristics and smoking habits.

The key strengths of this actual use study included (1) the high ecological validity due to the near to real-world setting of the study, (2) the broad regional coverage, (3) the large sample size, and (4) the duration of the observational period of six weeks (which is slightly longer than in previous studies of alternative tobacco products[70,71]).

Limitations include the fact that due to the study having been conducted in a pre-market setting, the study participants did not pay for the THS products, while they continued to pay for their cigarettes, which may have overestimated the level of THS adoption in this study. While important insights were generated regarding the group of current adult daily smokers who participated in the study, the sample was not representative of the U.S. adult smoker population, which should be considered when interpreting the results. Finally, no biochemical verification of tobacco consumption, such as CO monitoring, was used, as the method of data collection relied exclusively on self-reported tobacco consumption. With regard to this point, it should be noted that validation studies have shown that self-reported tobacco consumption behaviors among adults are consistent and reliable[55,72].

Factors that were not measured may have influenced THS adoption (e.g., repeated exposure to product communication, peer-to-peer information sharing, risk perception [the product possibly being perceived as possible risk-reduced], familiarity, and acceptability of alternative tobacco usage behavior, as it may develop once the product has been marketed for some time)[73].

In view of the above limitations, post-market studies are needed to provide actual levels and drivers of THS adoption and use patterns once THS is commercially marketed in the U.S. Consistent with several theoretical frameworks that have been used to understand the impact of intervention or prevention policies[74,75], research should not only look at factors intrinsic to the users or to the product to explain use behavior but also take into consideration the influence of social (e.g., family background, peer influence) and societal/environmental factors (e.g., media influence, public health policy).

Conclusions
This actual use study showed that after a six week period of *ad libitum* use of THS provided at no expense, almost 15% of U.S. daily adult smokers in the sample replaced 70% or more of their tobacco consumption with THS. The main predictors of THS adoption were positive sensory assessment and the ease of use. Socio-demographic characteristics and smoking habits appeared much less important. The findings suggest that the introduction of THS in the U.S. has the potential to result in adoption by adult smokers who would otherwise continue to smoke cigarettes. On the basis of this adoption rate, this could benefit public health by having a positive impact on this particular population of adult smokers[76]. In particular,

the results indicate that the adoption of THS is unlikely to result in an increase of tobacco consumption. Epidemiologic and post-marketing studies can provide further insights on the levels and the drivers of THS adoption and the use patterns of the THS to allow to assess the impact of the THS at the individual and the overall population level.

Data availability

Underlying data

Open Science Framework: Potential predictors of adoption of the Tobacco Heating System (THS) by U.S. adult smokers. https://doi.org/10.17605/OSF.IO/SBDXG[59].

This project contains the following underlying data files:

- Raw dataset.sas

- Variable Coding Book.pdf

Extended data

Open Science Framework: Potential predictors of adoption of the Tobacco Heating System (THS) by U.S. adult smokers. https://doi.org/10.17605/OSF.IO/SBDXG[76].

This project contains the following extended data files:

- Brochure.pdf

Data are available under the terms of the Creative Commons Zero "No rights reserved" data waiver (CC0 1.0 Public domain dedication).

References

1. National Center for Chronic Disease Prevention, Health Promotion Office on Smoking and Health: **The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General**. Reports of the Surgeon General, Atlanta (GA): Centers for Disease Control and Prevention (US); 2014.
PubMed Abstract

2. Danaei G, Ding EL, Mozaffarian D, *et al.*: **The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors.** *PLoS Med.* 2009; **6**(4): e1000058.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

3. Jha P, Ramasundarahettige C, Landsman V, *et al.*: **21st-century hazards of smoking and benefits of cessation in the United States.** *N Engl J Med.* 2013; **368**(4): 341–350.
PubMed Abstract | **Publisher Full Text**

4. National Center for Health Statistics (US): **Health, United States, 2016: With Chartbook on Long-term Trends in Health**. ((US) NCfHS ed. Hyattsville (MD); 2017.
PubMed Abstract

5. Gottlieb S, Zeller M: **A Nicotine-Focused Framework for Public Health.** *N Engl J Med.* 2017; **377**(12): 1111–1114.
PubMed Abstract | **Publisher Full Text**

6. U.S. Department of Health and Human Services: **FDA announces comprehensive regulatory plan to shift trajectory of tobacco-related disease, death**. In *News Release, July 28 2017*. 2017.
Reference Source

7. IOM (Institute of Medicine): **Scientific standards for studies on modified risk tobacco products**. Washington, DC: The National Academies Press. 2012.
Publisher Full Text

8. Zeller M, Hatsukami D; Strategic Dialogue on Tobacco Harm Reduction Group: **The Strategic Dialogue on Tobacco Harm Reduction: a vision and blueprint for action in the US.** *Tob Control.* 2009; **18**(4): 324–332.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

9. Institute of Medicine Committee to Assess the Science Base for Tobacco Harm R: **Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction**. Edited by Stratton K, Shetty P, Wallace R, Bondurant S. Washington (DC): National Academies Press (US), Copyright 2001 by the National Academy of Sciences. All rights reserved.; 2001.
Publisher Full Text

10. World Health Organization (WHO): **Monograph: advancing knowledge on regulating tobacco products**. Geneva: World Health Organization; 2009.
Reference Source

11. Royal College of Physicians: **Harm reduction in nicotine addiction: helping people who can't quit**. A report by the Tobacco Advisory Group of the Royal College of Physicians. London: RCP; 2007.
Reference Source

12. Single E: **Defining harm reduction.** *Drug Alcohol Rev.* 1995; **14**(3): 287–290.
PubMed Abstract | **Publisher Full Text**

13. Abrams DB, Glasser AM, Pearson JL, *et al.*: **Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives.**

Annu Rev Public Health. 2018; **39**: 193–213.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

14. Kozlowski LT, Abrams DB: **Obsolete tobacco control themes can be hazardous to public health: the need for updating views on absolute product risks and harm reduction.** *BMC Public Health.* 2016; **16**: 432.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

15. FDA (Food and Drug Administration): **Guidance for industry - Modified risk tobacco product applications - Draft Guidance**. 2012.
Reference Source

16. Berman ML, Connolly G, Cummings KM, *et al.*: **Providing a Science Base for the Evaluation of Tobacco Products.** *Tob Regul Sci.* 2015; **1**(1): 76–93.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

17. Mallock N, Böss L, Burk R, *et al.*: **Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks.** *Arch Toxicol.* 2018; **92**(6): 2145–2149.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

18. McNeill A, Brose LS, Calder R, *et al.*: **Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England**. 2018.
Reference Source

19. Philip Morris International Inc. (PMI): **2021 First-Quarter Results April 20, 2021**.
Reference Source

20. US Food and Drug Administration: **22nd Century Group Inc. modified risk tobacco product (MRTP) applications**.
Reference Source

21. US Food and Drug Administration: **FDA Authorizes Marketing of IQOS Tobacco Heating System with 'Reduced Exposure' Information**.
Reference Source

22. US Food and Drug Administration: **FDA grants first-ever modified risk orders to eight smokeless tobacco products**.
Reference Source

23. US Food and Drug Administration: **R.J. Reynolds Tobacco Company modified risk tobacco product (MRTP) applications**.
Reference Source

24. US Food and Drug Administration: **US Smokeless Tobacco Company modified risk tobacco product (MRTP) application**.
Reference Source

25. Smith MR, Clark B, Lüdicke F, *et al.*: **Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the system and the scientific assessment program.** *Regul Toxicol Pharmacol.* 2016; **81 Suppl 2**: S17–S26.
PubMed Abstract | **Publisher Full Text**

26. Oviedo A, Lebrun S, Kogel U, *et al.*: **Evaluation of the Tobacco Heating System 2.2. Part 6: 90-day OECD 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects of a mentholated version compared with mentholated and non-mentholated cigarette smoke.** *Regul Toxicol Pharmacol.* 2016; **81 Suppl 2**: S93–S122.
PubMed Abstract | **Publisher Full Text**

27. Kogel U, Titz B, Schlage WK, *et al.*: **Evaluation of the Tobacco Heating System 2.2. Part 7: Systems toxicological assessment of a mentholated version revealed reduced cellular and molecular exposure effects compared with mentholated and non-mentholated cigarette smoke.** *Regul Toxicol Pharmacol.* 2016; **81 Suppl 2**: S123–S138.
PubMed Abstract | **Publisher Full Text**

28. Schaller JP, Pijnenburg JPM, Ajithkumar A, *et al.*: **Evaluation of the Tobacco Heating System 2.2. Part 3: Influence of the tobacco blend on the formation of harmful and potentially harmful constituents of the Tobacco Heating System 2.2 aerosol.** *Regul Toxicol Pharmacol.* 2016; **81 Suppl 2**: S48–S58.
PubMed Abstract | **Publisher Full Text**

29. Schaller JP, Keller D, Poget L, *et al.*: **Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol.** *Regul Toxicol Pharmacol.* 2016; **81 Suppl 2**: S27–S47.
PubMed Abstract | **Publisher Full Text**

30. Sewer A, Kogel U, Talikka M, *et al.*: **Evaluation of the Tobacco Heating System 2.2 (THS2.2). Part 5: microRNA expression from a 90-day rat inhalation study indicates that exposure to THS2.2 aerosol causes reduced effects on lung tissue compared with cigarette smoke.** *Regul Toxicol Pharmacol.* 2016; **81 Suppl 2**: S82–S92.
PubMed Abstract | **Publisher Full Text**

31. Wong ET, Kogel U, Veljkovic E, *et al.*: **Evaluation of the Tobacco Heating System 2.2. Part 4: 90-day OECD 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects compared with cigarette smoke.** *Regul Toxicol Pharmacol.* 2016; **81 Suppl 2**: S59–S81.
PubMed Abstract | **Publisher Full Text**

32. Martin F, Talikka M, Ivanov NV, *et al.*: **Evaluation of the tobacco heating system 2.2. Part 9: Application of systems pharmacology to identify exposure response markers in peripheral blood of smokers switching to THS2.2.** *Regul Toxicol Pharmacol.* 2016; **81 Suppl 2**: S151–S157.
PubMed Abstract | **Publisher Full Text**

33. Haziza C, de La Bourdonnaye G, Skiada D, *et al.*: **Evaluation of the Tobacco Heating System 2.2. Part 8: 5-Day randomized reduced exposure clinical study in Poland.** *Regul Toxicol Pharmacol.* 2016; **81 Suppl 2**: S139–S150.
PubMed Abstract | **Publisher Full Text**

34. Breheny D, Adamson J, Azzopardi D, *et al.*: **A novel hybrid tobacco product that delivers a tobacco flavour note with vapour aerosol (Part 2): *In vitro* biological assessment and comparison with different tobacco-heating products.** *Food Chem Toxicol.* 2017; **106**(Pt A): 533–546.
PubMed Abstract | **Publisher Full Text**

35. Eaton D, Jakaj B, Forster M, *et al.*: **Assessment of tobacco heating product THP1.0. Part 2: Product design, operation and thermophysical characterisation.** *Regul Toxicol Pharmacol.* 2018; **93**: 4–13.
PubMed Abstract | **Publisher Full Text**

36. Forster M, Fiebelkorn S, Yurteri C, *et al.*: **Assessment of novel tobacco heating product THP1.0. Part 3: Comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions.** *Regul Toxicol Pharmacol.* 2018; **93**: 14–33.
PubMed Abstract | **Publisher Full Text**

37. Gale N, McEwan M, Eldridge AC, *et al.*: **A randomised, controlled, two-Centre open-label study in healthy Japanese subjects to evaluate the effect on biomarkers of exposure of switching from a conventional cigarette to a tobacco heating product.** *BMC Public Health.* 2017; **17**(1): 673.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

38. Jaunky T, Adamson J, Santopietro S, *et al.*: **Assessment of tobacco heating product THP1.0. Part 5: *In vitro* dosimetric and cytotoxic assessment.** *Regul Toxicol Pharmacol.* 2018; **93**: 52–61.
PubMed Abstract | **Publisher Full Text**

39. Taylor M, Thorne D, Carr T, *et al.*: **Assessment of novel tobacco heating product THP1.0. Part 6: A comparative *in vitro* study using contemporary screening approaches.** *Regul Toxicol Pharmacol.* 2018; **93**: 62–70.
PubMed Abstract | **Publisher Full Text**

40. Thorne D, Breheny D, Proctor C, *et al.*: **Assessment of novel tobacco heating product THP1.0. Part 7: Comparative *in vitro* toxicological evaluation.** *Regul Toxicol Pharmacol.* 2018; **93**: 71–83.
PubMed Abstract | **Publisher Full Text**

41. Auer R, Concha-Lozano N, Jacot-Sadowski I, *et al.*: **Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name.** *JAMA Intern Med.* 2017; **177**(7): 1050–1052.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

42. Davis B, Williams M, Talbot P: **iQOS: evidence of pyrolysis and release of a toxicant from plastic.** *Tob Control.* 2019; **28**(1): 34–41.
PubMed Abstract | **Publisher Full Text**

43. Li X, Luo Y, Jiang X, *et al.*: **Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes.** *Nicotine Tob Res.* 2019; **21**(1): 111–118.
PubMed Abstract | **Publisher Full Text**

44. Farsalinos KE, Yannovits N, Sarri T, *et al.*: **Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette.** *Addiction.* 2018; **113**(11): 2099–2106.
PubMed Abstract | **Publisher Full Text**

45. Bekki K, Inaba Y, Uchiyama S, *et al.*: **Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes.** *J UOEH.* 2017;

39(3): 201–207.
PubMed Abstract | **Publisher Full Text**

46. Caruso M, Polosa R: **Perplexing Conclusions Concerning Heat-Not-Burn Tobacco Cigarettes.** *JAMA Intern Med.* 2017; **177**(11): 1699.
PubMed Abstract | **Publisher Full Text**

47. Food and Drug Administration (FDA): **FDA Briefing Document- January 24-25, 2018 Meeting of the Tobacco Products Scientific Advisory Committee (TPSAC) - Modified Risk Tobacco Product Applications (MRTPAs), MR0000059-MR0000061 Philip Morris Products S.A.** 2018.
Reference Source

48. 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.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

49. Tabuchi T, Kiyohara K, Hoshino T, *et al.*: **Awareness and use of electronic cigarettes and heat-not-burn tobacco products in Japan.** *Addiction.* 2016; **111**(4): 706–713.
PubMed Abstract | **Publisher Full Text**

50. **Guidance for Industry – Modified Risk Tobacco Product Applications (Draft Guidance)**.
Reference Source

51. Food and Drug Administration (FDA): **Guidance for industry - Label comprehension studies for nonprescription drug products.** 2010.
Reference Source

52. Leonard-Segal A, Shay LE, Shetty D, *et al.*: **Unique role of consumer studies in nonprescription drug development.** *J Am Pharm Assoc (2003).* 2009; **49**(5): 670–673.
PubMed Abstract | **Publisher Full Text**

53. Brass EP, Shay LE, Leonard-Segal A: **Analysis of multiple end points in consumer research in support of switching drugs from prescription to over-the-counter status: the concept of end-point hierarchies.** *Clin Pharmacol Ther.* 2009; **85**(4): 369–374.
PubMed Abstract | **Publisher Full Text**

54. Burris JL, Carpenter MJ, Wahlquist AE, *et al.*: **Brief, instructional smokeless tobacco use among cigarette smokers who do not intend to quit: a pilot randomized clinical trial.** *Nicotine Tob Res.* 2014; **16**(4): 397–405.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

55. Pearson JL, Elmasry H, Das B, *et al.*: **Comparison of Ecological Momentary Assessment Versus Direct Measurement of E-Cigarette Use With a Bluetooth-Enabled E-Cigarette: A Pilot Study.** *JMIR Res Protoc.* 2017; **6**(5): e84.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

56. Pearson JL, Smiley SL, Rubin LF, *et al.*: **The Moment Study: protocol for a mixed method observational cohort study of the Alternative Nicotine Delivery Systems (ANDS) initiation process among adult cigarette smokers.** *BMJ Open.* 2016; **6**(4): e011717.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

57. **Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications**.
Reference Source

58. Hoffmann W, Latza U, Baumeister SE, *et al.*: **Guidelines and recommendations for ensuring Good Epidemiological Practice (GEP): a guideline developed by the German Society for Epidemiology.** *Eur J Epidemiol.* 2019; **34**(3): 301–317.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

59. Roulet S: **Potential Predictors of Adoption of the Tobacco Heating System (THS) by U.S. Adult Smokers.** *OSF.* 2019.
http://www.doi.org/10.17605/OSF.IO/SBDXG

60. Roulet S, Mainy N, Chrea C, *et al.*: **Pre-market studies from five countries in Asia and Europe to measure the adoption of the tobacco heating system (THS) in smokers.** *Tobacco Science Technology.* 2017; **50**(13): 86–96.
Reference Source

61. Akaike H: **A new look at the statistical model identification.** *IEEE Trans Automat Contr.* 1974; **19**(6): 716–723.
Publisher Full Text

62. Litt MD, Duffy V, Oncken C: **Cigarette smoking and electronic cigarette vaping patterns as a function of e-cigarette flavourings.** *Tob Control.* 2016; **25**(Suppl 2): ii67–ii72.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

63. Farsalinos KE, Romagna G, Tsiapras D, *et al.*: **Impact of flavour variability on electronic cigarette use experience: an internet survey.** *Int J Environ Res Public Health.* 2013; **10**(12): 7272–7282.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

64. Meier E, Isaksson Vogel R, O'Connor RJ, *et al.*: **Preference for Flavored Noncombustible Nicotine Products Among Smokers Motivated to Switch From Cigarettes.** *Nicotine Tob Res.* 2016; **18**(5): 892–893.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

65. Pepper JK, Ribisl KM, Emery SL, *et al.*: **Reasons for starting and stopping electronic cigarette use.** *Int J Environ Res Public Health.* 2014; **11**(10): 10345–10361.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

66. Kralikova E, Novak J, West O, *et al.*: **Do e-cigarettes have the potential to compete with conventional cigarettes?: a survey of conventional cigarette**

smokers' experiences with e-cigarettes. *Chest.* 2013; **144**(5): 1609–1614.
PubMed Abstract | **Publisher Full Text**

67. Etter JF: **Electronic cigarettes: a survey of users.** *BMC Public Health.* 2010; **10**: 231.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

68. Kong G, Morean ME, Cavallo DA, *et al.*: **Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults.** *Nicotine Tob Res.* 2015; **17**(7): 847–854.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

69. Levy DT, Yuan Z, Li Y: **The Prevalence and Characteristics of E-Cigarette Users in the U.S.** *Int J Environ Res Public Health.* 2017; **14**(10): E1200.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

70. Polosa R, Caponnetto P, Morjaria JB, *et al.*: **Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study.** *BMC Public Health.* 2011; **11**: 786.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

71. Burris JL, Wahlquist AE, Alberg AJ, *et al.*: **A longitudinal, naturalistic study of U.S. smokers' trial and adoption of snus.** *Addict Behav.* 2016; **63**: 82–88.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

72. Soulakova JN, Hartman AM, Liu B, *et al.*: **Reliability of adult self-reported smoking history: data from the tobacco use supplement to the current population survey 2002-2003 cohort.** *Nicotine Tob Res.* 2012; **14**(8): 952–960.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

73. Pepper JK, Emery SL, Ribisl KM, *et al.*: **How risky is it to use e-cigarettes? Smokers' beliefs about their health risks from using novel and traditional tobacco products.** *J Behav Med.* 2015; **38**(2): 318–326.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

74. Fong GT, Cummings KM, Borland R, *et al.*: **The conceptual framework of the International Tobacco Control (ITC) Policy Evaluation Project.** *Tob Control.* 2006; **15 Suppl 3**: iii3–11.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

75. Hyland A, Ambrose BK, Conway KP, *et al.*: **Design and methods of the Population Assessment of Tobacco and Health (PATH) Study.** *Tob Control.* 2017; **26**(4): 371–378.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

76. Djurdjevic S, Lee PN, Weitkunat R, *et al.*: **Modeling the Population Health Impact of Introducing a Modified Risk Tobacco Product into the U.S. Market.** *Healthcare (Basel).* 2018; **6**(2): E47.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

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Reviewer Report 11 September 2019

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✅ **Fabrizio Messina**
BAT (Investments) Limited, Southampton, UK
Krishna Prasad
[1] Research and Development, British American Tobacco, Southampton, UK
[2] BAT (Investments) Limited, Southampton, UK

This paper reports the outcome from an 'actual use' study designed to determine if users are likely to use the product in a manner that reduces their individual health risks or exposures as compared to using other commercially marketed tobacco products. Actual use studies should allow consumers to interact freely with the product in real world conditions.

The study design, recruitment, methodology, data collection, analysis and results are well presented. However, some of the conclusions drawn are broad and statistical procedures used are unconventional, leading to interpretation based on variable selection criteria. Given the recruitment limitation of not having recruited non-tobacco users, the conclusions drawn should be limited to THS adoption among current smokers in the US.

Abstract
The objective of the study is stated twice in the background.
Observational studies by their very nature observe individuals without manipulation or intervention. In this study the participants are asked to use the test products instead of their regular products, therefore, should be referred to as actual use study.

There is little if any data regarding the use of e-cigarettes, cigars etc. in the body of the paper. Number and type of participants and brief inclusion/exclusion criteria would make the methods section more informative.

Whilst I understand that it is not for the paper to make policy implications, it would be useful to draw on the adoption of THS by vulnerable groups in conclusions.

Introduction

Generally, the introduction is well presented with relevant references from the literature. Reference to actual use studies with similar tobacco heating system would enhance the articles and provide basis for comparison in discussion.

Despite acknowledging that most actual use studies for cMRTP have been conducted in artificial setting and provided free, the products were provided free in this study.

Methods
The methods used are clearly presented with reference to sample size calculation, inclusion/exclusion criteria, products, data collection and analysis.

Rationale for some of the criteria for example, exclusion of individuals who had started smoking with in the last 30 days would have helped.

Sample Size Calculation
Based on the reference in the paper (Dhand, N. K., & Khatkar, M. S. (2014)). Calculating the sample size
$n \geq (1.96/0.05)^2 *0.5 \times 0.5 = 384.16$ and allowing for an attrition rate of 40%, I arrive at $384.16*(1/(1 - 0.4))= 641$.
In this paper they have recruited 1300 which is almost double as 641.

Pre-screening of the regressors
I understand the practice of pre-screening the regressors to understand the relation between the dependent and the independent variables, however, excluding regressors based on an arbitrary rule (p-value <=0.2), it's rather unconventional.
According to "Five myths about variable selection" by Georg Heinze & Daniela Dunkler[1]: "While it is true that regression coefficients are often larger in univariable models than in multivariable ones, also the opposite may occur, if some variables (with all positive effects on the outcome) are negatively correlated. Moreover, univariable prefiltering, sometimes also referred to as "bivariable analysis," does not add stability to the selection process as it is based on stochastic quantities and can lead to overlooking important adjustment variables needed for control in an etiologic model. Although univariable prefiltering is traceable and easy to do with standard software, one should better completely forget about it as it is neither a prerequisite nor providing any benefits when building multivariable models (*Sung et al 1996*[2]*.*"

If the authors have not already run the logistic regression including all the regressors, it is worth re-running to see if we observe different potential predictors.
   ○ The study participants were asked to report the current use of NRT products – despite selecting smokers who had no intention to quit. What was reasons for them using NRT?

   ○ The main outcome measure was self-reported consumption of cigarettes and THS, does not take into account e-cig or NRT use - this would likely influence the number of THS sticks used and therefore inflate the ratio?
Results
   ○ Is the decrease in the number of tobacco products (Table 2) significant? Given the large SDs I suggest they are not different.
Discussion
   ○ Can you say that THS is a viable alternative if 85% of users rejected the offer even when

given the product for free?

- ○ "availability of THS is unlikely to prevent those willing to quit tobacco from doing so". Can you really make this statement from the data provided? 'Previous quit attempts' is different from 'intention to quit'.

- ○ "almost 15% of U.S. daily adult smokers substituted cigarettes with THS". While this is technically true, they didn't substitute completely which may be incorrectly inferred from this conclusion.

References
1. Heinze G, Dunkler D: Five myths about variable selection.*Transpl Int*. 2017; **30** (1): 6-10 PubMed Abstract | Publisher Full Text
2. Sun GW, Shook TL, Kay GL: Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis.*J Clin Epidemiol*. 1996; **49** (8): 907-16 PubMed Abstract | Publisher Full Text

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: I am a full time employee of British American Tobacco and coordinator for the CORESTA (Cooperation Centre for Scientific Research Relative to Tobacco) product use behaviour (PUB) sub-group.

Reviewer Expertise: I have several years' experience in tobacco and nicotine products use behaviour. As part of my current role I look after all human studies from mouth level exposure, puffing topography, consumer risk perception and post market surveillance.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 20 Jun 2021

Christelle Chrea, Philip Morris Products S.A., Neuchatel, Switzerland

Abstract
The Abstract has been slightly edited according to the Reviewers' comment on its structure, with no alteration to the message presented. (i.e. removed repetitious sentences, as well as addition, restructuration and move of sentences to a different part of the abstract for clarity, etc...). As suggested, the number of participants together with the description of the participants (i.e. current adult smokers) is now included in the Abstract. The full description of inclusion/exclusion criteria remains included under Participants subsection of the Methods.
The Reviewers indicated that because the participants are asked to use the test products instead of their regular products, it should be referred to as an actual use study in the Abstract. We fully agree with this statement and, actually, the manuscript title "Potential predictors of adoption of the Tobacco Heating System by U.S. adult smokers: An actual use study" clearly reflects that it is an actual use study. The terminology of "observational study" is also being used to refer to the fact that, there was no intervention with the study population beyond providing the THS product. Moreover, study participants were not asked to use the THS product during the entire study periods (i.e. baseline and observational periods); they were only requested "to make an entry into an e-diary every time they consumed a cigarette during the 1-week baseline period and a HeatStick or a cigarette during the 6-week observational period of the study. Participants were also requested to indicate on a daily basis using the e-diary whether or not they used other products containing nicotine (i.e. e-cigarettes, nicotine replacement therapy products, and other tobacco products such as cigars, cigarillos and smokeless tobacco products)."
The Reviewers suggested to further expand our conclusions and draw on the adoption of THS by vulnerable groups. THS is aimed at current adult smokers who would otherwise continue to smoke combustible cigarettes and represent the study population of this actual use study. Therefore, we believe that drawing any conclusion from this study regarding vulnerable groups is beyond the scope of this publication.

The Reviewer noted that the data about the use of e-cigarettes, cigars and other tobacco products than cigarettes, is not extensively covered in our manuscript. This is because the Tobacco Heating System is aimed at current adult smokers who would otherwise continue to smoke cigarettes and hence the focus of this publication is on THS and cigarettes. Data about e-cigarette use has been captured during the rescreening phase (yes/no) and show that "the proportion of participants adopting THS was higher among e-cigarette adult users (23.1% vs. 14.1%)". Data about e-cigarette use, as well as nicotine replacement therapy products, and other tobacco products such as cigars, cigarillos, and smokeless tobacco products, has also been captured during the baseline and the observational periods. The data show that between the baseline and the end of the observational period, the usage of nicotine replacement therapy products remained stable, while the usage of e-cigarettes increased and the usage of other tobacco products such as cigars, cigarillos and smokeless tobacco products decreased.

Introduction
The Reviewers outlined that reference to actual use studies with a similar tobacco heating

system (THS) would enhance the articles and provide basis for comparison in discussion. While we agree with this comment, we are not aware of any other premarket actual use study regarding another heated tobacco product (i.e. beyond the THS).

Regarding the study settings, the studies referenced in Introduction which collected data on potential MRTPs were performed in an artificial setting because there was an intervention (i.e. participants being instructed to adopt a given behavior), which was not the case for our study. We slightly edited the related sentence to clarify that for these studies, the MRTP was also provided for free, as it was also the case for our pre-market study. This aspect of the study design has been stated as a study limitation in the Discussion section of the manuscript, which states, "Limitations include the fact that due to the study having been conducted in a pre-market setting, the study participants did not pay for the THS products, while they continued to pay for their cigarettes, which may have overestimated the level of THS adoption in this study."

Methods

The Reviewer requested further insights regarding the rationale for some of the inclusion/exclusion criteria, in particular concerning the exclusion of individuals who had started smoking within the last 30 days. This exclusion criteria was applied to ensure that participants involved in the study have been smoking cigarettes for a certain period of time, and thus, have a relatively established product use pattern (of using cigarettes, in this particular case).

The Reviewers provided a correct sample size calculation (i.e. 641 participants). Additionally to the number of 641, we assumed that we will have 50% "starters" ("starters" are those subjects who used 100 or more HeatSticks during the observational period) in the sample in addition to the 40% related to the attrition rate, which doubles the calculated number. Thus, we recruited 1300 participants.

To the Reviewers comments on pre-screening of the regressors, we saw that different authors have favored different variable selection strategies. We have chosen this procedure to have sufficient degree of freedoms to estimate the effects. It seems unlikely that the variables in our dataset with p>0.2 in the bivariate analysis will have an additional influence.

The Reviewers formulated questions regarding reasons for participants using NRT and whether number of HeatSticks used could have been influenced by use of e-cigarettes and NRT. The main data for this manuscript was the number of cigarettes and the number of HeatSticks used by study participants over a 6-week period. Information related to the use of e-cigarettes, cigars etc. can be found as part of the study report, which is publicly available as part of Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications and can be accessed through the following link: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications. The percentage of NRT use was 0.1% at rescreening, which indicates that it is highly unlikely to have any impact on the number of HeatSticks used. The percentage of e-cigarette use was 5.3% at rescreening so relatively small, and hence, unlikely to have any significant impact on the number of HeatSticks used.

Results

The Reviewers commented on the potential significance of the decrease in the number of tobacco products presented in Table 2. Actually, the results are reported in means without any statistical test.

Discussion

The Reviewers asked whether stating that THS is a viable alternative was appropriate with 85% of users rejecting the offer even when given the product for free. We believe that THS is a viable alternative as about 15% of current adult smokers' participants have replaced 70% or more of their tobacco consumption (cigarettes + THS) by THS. Further analysis has shown that about 6% (n = 968) of adult smokers' participants completely stopped smoking combustible cigarette (i.e. THS constituted 100% of their tobacco consumption).

As per the Reviewers comment regarding previous quit attempts and intention to quit, the manuscript has been amended to address your comment as follows: the old text "Participants who had previously attempted to quit smoking were less likely to adopt THS than participants who never attempted to quit smoking in the past. This finding suggests that the availability of THS is unlikely to prevent those willing to quit tobacco from doing so. This is further confirmed by the fact that the intention to quit smoking within the next six months was not associated with THS adoption," was replaced with "Participants who never attempted to quit smoking in the past were more likely to adopt THS than participants who had previously attempted to quit smoking. Intention to quit smoking within the next six months was not associated with THS adoption suggesting that the availability of THS is unlikely to interfere with intention to quit smoking."

When it comes to cigarettes substituted with THS for study participants, the manuscript has been amended as follows: the old text "Almost 15% of U.S. daily adult smokers substituted cigarettes with THS" was replaced with "almost 15% of U.S. daily adult smokers replaced 70% or more of their tobacco consumption with THS".

Competing Interests: No competing interests were disclosed.

Reviewer Report 02 September 2019

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? **Riccardo Polosa**
[1] Centre for the Prevention and Treatment of Tobacco Addiction (CPCT), Teaching Hospital "Policlinico-V. Emanuele", University of Catania, Catania, Italy
[2] Center of Excellence for the acceleration of Harm Reduction, University of Catania, Catania, Italy

In this 6-weeks observational study, self-reported stick-by-stick consumption of IQOS was assessed and potential predictors of product adoption identified. Understanding predictors of e-cig/THP adoption is important as it may lead to improved smoking cessation/reduction rates. I have the following comments:

Major Comments

Recruiting method is a potential (and probable) source of bias. As noted by the Authors, market panel members are not a representative sample of the population of US smokers. The participant remuneration was significantly high ($440); this - together with the fact that IQOS and consumables were given for free - would encourage participation and spin study findings. All the above casts doubts on whether the study is really conducted under real-world setting conditions and jeopardize the main goal of the study, which was to describe IQOS adoption in a real-world setting.

The study should be better reported.
- No report of refusal to participate.

- No report of partial compliance with diary reporting.

- No report of the number non-compliant with interview schedule.

- No report of the number not turning in study materials (used for measurement, so significant).

- The only report is the number of participants who made no diary entries, and that alone is significant as 28% made no entries. If the authors conducted imputations for missing data (and certainly there were some missing data points!) this should be reported.

I have concerns about the Analyses.
- E-cig users made up 12 of the 141 adopters, but represented only 5.4% of the population - clearly skewing the results. E-cig use should have been analyzed as a confounder.

- The combined use categories make little sense to me.

- The effectiveness for Hispanics/Latinos barely reached significance.

- Wide CIs indicate that there are insufficient numbers for subgroup analysis.

Can you clarify which version of the product was provided in this study; as far as I am aware the manufacturer has rolled out the third generation/evolution of IQOS. This is important for the interpretation of study findings (I was told that newer generations perform substantially better than earlier generations).

Findings are products specific. It would have been interesting to have another comparator (e-cigs?) in the study in order to have a better understanding in terms of predictors of adoption of these new technologies. This should be discussed.

There's lack of information about complete abstinence from tobacco cigarettes and this should be provided.

Minor Comments

Introduction, Page 3. *"These findings suggest that the large majority of IQOS users in Japan switched from cigarettes to IQOS and that there is minimal uptake from nonsmokers".* Please qualify these statements with appropriate numbers/percentages (and references).

The authors state that the study supplied a hotline for information and to collect reports of adverse effects. How many calls did the hotline receive? What adverse effects were reported? This is critical information and should be provided in the paper.

Study design. Is there a psychological behavioural pharmacological theory/rationale for the chosen length of study periods (i.e. 1 week for baseline period; 6 weeks for observation period)?

I note that a validated psycho-diagnostic tool was used to measure participants' intention to quit. Please specify which one.

More information on the structure and validity of the questionnaires used are need and the questionnaires should be included in the appendix.

It would have been equally important to evaluate the construct of the intention to switch to low-risk products.

An important predictor for IQOS adoption could have been the participants own cigarette brand.

I was sorry to see in the analysis that heavy smokers (21+/day) were less likely to adopt than light smokers. This may reflect high level of inefficiency of (currently marketed) IQOS to adequately reproduce the experience in cigarette smoking. This should be discussed.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Partly

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
Partly

Competing Interests: RP has received lecture fees and research funds from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has also served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, ECITA (Electronic Cigarette Industry Trade Association, in the UK), Arbi Group Srl., and Health Diplomats. RP is the Director of the Center of Excellence for the acceleration of Harm Reduction at the University of Catania

(CoEHAR), which has received a grant from Foundation for a Smoke Free World to support 8 research projects. RP is also currently involved in the following pro bono activities: scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti-Smoking League)and Chair of the European Technical Committee for standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4).

Reviewer Expertise: Tobacco research (including ECIG and THP)

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Jun 2021

Christelle Chrea, Philip Morris Products S.A., Neuchatel, Switzerland

<u>**Major comments**</u>
The Reviewer questioned the recruitment method and the extent to which our study should be considered to have been conducted under real-world setting conditions. From our perspective, an Actual Use Study represents the most appropriate study design to approximate real-world conditions in a premarket environment (i.e. in a condition in which the investigational product has not been authorized to be marketed, and therefore, is not commercially available to the public yet). Therefore, such study attempts to replicate to the maximum possible extent within the boundaries determined by the pre-market conditions and the limits imposed by feasibility.
With respect to the recruiting method, we would like to note that the rationale for the selection of a non-probabilistic sample was to ensure the feasibility of the study. The sample was large as more than 1,300 participants were enrolled in the study and the results were robust as the study was conducted in eight different sites spread across the U.S.

We chose these eight geographical locations to: i) recruit a diverse population of current U.S. adult daily smokers study participants; ii) allow distribution of the product, considering the various state requirements (e.g., retail license, tax stamping by a licensed distributer, pre-notification to fire Marshall); and iii) to ensure a good control over the investigational product. Although results are not generalizable to the U.S. smoking population, they provide a robust description of the patterns of use.

Concerning the participants remuneration, we believe that participants were reimbursed adequately for their time and effort. The compensation was based on the study duration and the numerous tasks that they were asked to perform, e.g., complete an e-diary on a stick-by-stick frequency, answer to CATI interviews, go to the study site to get additional product, keep used and unused product, etc. Additionally, compensation in the study was up to $440, depending on the length of time in the study and return of the THS, used and unused *HeatSticks*, and the e-diary device. Assuming a full participation, this means $55 per week. To minimize the impact that reimbursement could have on participants' tobacco consumption, each participant was reimbursed only after the completion of the study. The amount of the compensation was approved by the Institutional Review Board (Sterling IRB)

and it was in line with the consumer research standards in the U.S. Finally, THS and *HeatSticks* were given for free, which is normal practice in consumer research, as stated by the ESOMAR code. We also note that other different features might have discouraged product use compared to a full real-world setting, e.g., lack of repeated communication, absence of a real customer care and presence of other adult users using the product. Having said that, we recognize that some of the points made by the Reviewer are the limitations of the study, which were inherent to the pre-market setting, and have been stated as such in the manuscript.

The Reviewer recommended to further report the overall disposition of subjects. The aim of this analysis was to assess the potential predictors of adoption of the Tobacco Heating System (THS) by current U.S. adult smokers after six weeks of THS product use. The data from this last week of the observational period (i.e. week 6) was therefore appropriate. In terms of the overall disposition of subjects, at pre-screening, 8,858 subjects, spread over eight sites (ranging from 599 in Denver to 2,050 in Detroit), were contacted via telephone. Of these, 21% initially refused to continue the telephone conversation. A certain proportion of the remaining subjects did not fulfill pre-specified criteria. The most common of these unfulfilled criteria were as follows: (i) participation in a consumer or clinical research study in the past three months (32%), (ii) being a non-daily adult smoker (18%), (iii) not willing to participate in a consumer research study that could last up to eight weeks (10%), (iv) started smoking regularly within the past 30 days (10%), (v) and demographic criteria above quota (10%). After this pre-screening phase, subjects were invited to one of the eight sites. At the eight sites 1,368 subjects were screened in person. Of the 1,368 screened subjects, 1,336 participants were enrolled, while 32 participants were not enrolled because of violation of inclusion or exclusion criteria. The number of participants screened was overall similar for each of the eight sites (ranging from 162 in Oklahoma City to 179 in Miami). The Full Analysis Set (FAS) comprised 1,106 participants, of which 119 prematurely discontinued and 987 completed the study. Overall, 230 subjects enrolled were not included in the FAS because they did not self-report in the e-diary "at least one documented consumption of a cigarette during the one-week baseline period" or "at least one documented consumption of a *HeatStick* during the six-week observational period." Moreover, no imputation of missing information was applied as part of the study. Those details can be found as part of the full study report, which is publicly available as part of Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications and can be accessed through the following link: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications.

The Reviewer formulated concerns about the analyses. The number of e-cigarette adult users is too small from our perspective to put into the logistic model (i.e. as a potential confounder) and the estimation of an effect would lead to wide Confidence Intervals (CIs). Regarding the effectiveness for Hispanics/Latinos, this is a true statement coming from the analysis. This means that this subgroup is no more likely than other subgroups to use THS; the reporting of the results was performed in line with the multivariate analysis, presented in Figure 2. The Reviewer outlined that wide CIs indicate that there are insufficient numbers for subgroup analysis. This is indeed correct as the planning of the sample size was not done for subgroup analysis.

Considering the potential inclusion of another comparator such as e-cigarettes, this suggestion from the Reviewer is interesting and we believe it merits potential exploration in studies designed and executed with a different purpose than a Modified Risk Tobacco Product Application. We have noticed that the Reviewer has designed such a study to compare changes in cigarette consumption and adoption rates among smokers randomized to either IQOS or e-cigarettes:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6962654/.

Regarding information about complete switching from cigarettes (i.e. 100% THS use), indeed, this information was not intended to be part of the manuscript, however, it has been provided during the Tobacco Products Scientific Advisory Committee review of Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications and can be accessed through the following link: https://www.fda.gov/media/110734/download. The percentage of 100% THS use (i.e. completely stopped using combustible cigarettes) was 6% at Week 6.

Under the Variables sub-section of the Methods, we provide the definition of the combined use category. To the Reviewer's comment about this category, we would like to outline that we have defined the product use categories with the objective of having a symmetrical classification, which allowed for practical and meaningful operationalized categorization, description and analysis. We have provided the raw data to allow scientists to create further categories.

Regarding the version of the product provided for the study, the Products sub-section of the Methods has been edited to indicate that the investigation product as part of this actual use study was the Tobacco Heating System Version 2.2. Thus, the product used in this study was an earlier version of the currently commercialized THS product.

Minor Comments

In the Introduction, the Reviewer suggested to qualify our statement "These findings suggest that the large majority of IQOS users in Japan switched from cigarettes to IQOS and that there is minimal uptake from nonsmokers" with numbers/percentages (and references). The findings come from several studies that are cited earlier in the text including their respective references (Tabuchi, 2017 and Tabuchi, 2016). Therefore, stating one particular percentage does not seem adequate as the statement is based on the overall weight of evidence rather than on particular percentage(s). We have added the references again along the statement. We also clarified that the preceding citation ("Analysis of predictors of IQOS current use (use in the previous 30 days) in 2017…") is linked to citation Tabuchi (2016) specifically.

The Reviewer indicated that data related to the hotline and adverse events (AEs) should be provided in the manuscript. However, safety was not a primary or secondary objective of this study. AEs spontaneously reported by study participants were collected using a passive safety surveillance methodology. The safety population exposed to the product use included the 1,158 participants who used at least one *HeatStick* and their data were valid for safety analysis. Overall, 121 AEs (102 non-serious and 19 serious) were reported in 48 individual cases. The overall reporting rate was 4.14%. The most frequent reported AEs by preferred terms (PTs) were Headache (n=13), Malaise (n=7), Nausea (n=6), Dizziness (n=4),

Abdominal discomfort (n=3), Oral discomfort (n=3), Chest pain (n=3), Cough (n=3), and Throat irritation (n=3). In total, the most frequent PTs represent 37.19% (45/121) of the total number of AEs reported during the study for all THS product variants. Headache was the most frequent reported AE in both product variants investigated in the study (reported in 13 out of 48 cases), with a reporting rate of 10.74% from all AEs received. Other frequent reported AEs were Malaise, Nausea and Dizziness (overall reporting rates from 3.30% to 5.78%). The severity of the leading event was reported as Mild in 5 cases (10.40%), Moderate in 7 cases (14.58%), Severe in 6 cases (12.50%), and Unknown in 6 cases (12.50%). The severity was not reported in half of the total number of cases (24 cases, 50.0%). Those details can be found as part of the full study report which is publicly available as part of Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications and can be accessed through following link: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications.

Regarding the study design and the chosen length of the observational period, the duration of six weeks was based on the assumption that participants would take between two and four weeks to either establish a regular pattern or to stop using *HeatSticks* altogether. The remaining weeks of the observational period would serve to confirm that *HeatSticks* usage patterns of participants have indeed stabilized. This study duration was also implemented by 22nd Century Group Inc. Modified Risk Tobacco Product (MRTP) Applications when conducting their actual use study pre-market. More information about 22nd Century Group Inc. Modified Risk Tobacco Product (MRTP) Applications can be accessed through the following link: https://www.fda.gov/tobacco-products/advertising-and-promotion/22nd-century-group-inc-modified-risk-tobacco-product-mrtp-applications.

The Reviewer recommended to provide further details on the structure and validity of the questionnaires used, including which measure was implemented to capture participants' intention to quit. The goal of our study was measure THS use patterns in current U.S. adult daily cigarette smokers and to assess THS product acceptance. Socio-demographics, smoking habits, sensory assessment, and ease of use were measured with ad-hoc questions. Consumption of cigarettes and THS were collected on self-reported stick-by-stick entry in an e-diary.

To capture intention to quit smoking, participants were asked to complete the Prochaska Stages of Change measure. Using a dichotomous response scale ('yes', 'no'), participants were first asked if they were seriously considering quitting smoking within the next six months. For those participants who indicated 'yes' for intention to quit smoking within the next six months, they were further asked if they were planning to quit smoking in the next 30 days. The Prochaska Stages of Change is based on the Prochaska and DiClemente stages of change concept, which is part of the Transtheoretical Model. The instrument assesses smokers' mental state for intention to quit smoking and enables categorization of smokers into the following three stages: 1) precontemplation (not thinking of quitting smoking), 2) contemplation (thinking of quitting smoking within the next six months), and 3) preparation (thinking of quitting smoking within the next 30 days). Of note, the measure of intention to quit smoking within the next 30 days was applied for the corresponding exclusion criteria. This is because THS is aimed at current adult smokers who would otherwise continue to smoke combustible cigarettes.

We also assessed intention to use THS as part of the inclusion criteria, however, measuring intention to switch to low-risk products in general was not performed. The full questionnaire (Case Report Form) can be found as part of the study report, which is publicly available as part of Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications and can be accessed through the following link: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications.

The Reviewer commented that the participants own cigarette brand could have been an important predictor for *IQOS* adoption. We did not collect the participants' own cigarette brand as part of the survey, so we could not include this variable in the analysis.

The Reviewer recommended to further discuss the results of the analyses for heavy smokers, i.e. the reduced adoption of THS among heavier smokers, and whether this may reflect high level of inefficiency of the product to adequately reproduce the experience in cigarette smoking. From our perspective, heavy adult smokers might simply need more time to adopt THS than current adult smokers who smoke fewer number of cigarettes per day.

Competing Interests: No competing interests were disclosed.

Reviewer Report 28 August 2019

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? **Kenneth A. Mundt**
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Summary

This article presents the methods and findings of a study in which a heated (not combusted) tobacco product (referred to as the Tobacco Heating System, or THS) was made available to current cigarette smokers who volunteered to participate and to maintain detailed diaries of their tobacco consumption, including cigarettes, THS, e-cigarettes, and any other nicotine-containing products. The study consisted of a one-week baseline period, six-weeks of observation, and one week 'close-out' period.

Participants were invited from a large market research database. Approximately 1300 participants enrolled, of which 1100 met the minimal cigarette and THS use criteria (one each) and by the end of the study 965 had completed diaries and were included in the statistical analyses. In addition to data on tobacco product consumption, participants provided information on socio-demographics

(sex, age, race/ethnicity, household information, marital status, educational attainment, occupation, income, etc.); smoking and tobacco use (number of cigarettes or THS or other products, intention to quit); and THS product assessment (taste, smell, aftertaste and ease of use).

Patterns of tobacco product use and changes over the six-week observation period were reported. Logistic regression with stepwise inclusion/elimination of variables (and first order interaction terms) was used to identify predictors of THS adoption (defined as >70% THS use). Participants of older age, selecting both THS flavors, users of and more favorable product assessment (taste and ease of use factors) and those never having attempted to quit were significantly more likely to adopt THS. Gender (not statistically significant) and ethnicity (statistically significant) contributed less.

Study strengths and weaknesses are well presented. The main strength was that this study closely monitored actual use of cigarettes and THS (and other nicotine products) over six weeks. One unavoidable limitation is that THS was provided to participants at no charge, and whether the observed patterns would be different if THS users were required to purchase their supplies.

General comments

This study generated several interesting and potentially helpful insights regarding real-world selection and use of THS among current conventional cigarette smokers. It appears to be the first study to provide such preliminary insights regarding how THS might be received in the United States.

The study methods, data collected, statistical analyses and results all are clearly presented. However, the discussion remains somewhat thin, i.e., individual analytical findings are addressed in succession, but the overall conclusion and integrated findings have not been fully explored. Interpretations of study findings should be compared more broadly with the published literature on other non-combusted tobacco or nicotine-containing products, as well as the possible impact of THS adoption among current smokers in the US. While important insights were generated regarding the group of smokers who volunteered for the study, no inference can be drawn with regard to non-tobacco users or users of other nicotine-containing products. The need for post-marketing studies is noted, but suggestions for their objectives (or specific research questions) are not offered. What specific additional studies would build on the initial findings reported here?

A more minor point: the text would benefit from careful editing to correct some grammatical errors and primarily to make it more idiomatic.

Specific comments

Abstract

The abstract needs improvement in content as well as structure.

Background: The final sentence presents the study aim; this largely is restated (with more detail) under the methods section. The reference to logistic regression reflects part of the study methods and should be moved.

Methods: The only information provided is that tobacco users were observed over six weeks. A brief but more informative overview of the study design would be helpful.
Results: This appears to be reasonably complete. Perhaps response rates (which were remarkably good) should be stated.

Conclusions: This section largely repeats results (and only some) and recommends post-marketing studies, but provides no interpretations, synthesis or policy implications based on this study.

Introduction

The introduction is informative and well presented.

Is it possible to provide some examples of MRTPs available in the US? Perhaps it would be helpful to clarify the status of e-cigarettes with respect to MRTPs.

Methods

The methods are clearly described. A few suggestions:

Setting: How or why were these study locations chosen? The reference to "Good Epidemiological Practice" should carry a citation, and perhaps be moved under Study Design.

Products: THS is described in greater detail here, and does not reflect any methods. Perhaps the description of the three components of the THS should be moved to the introduction where the THS is first described.

Data collection and measurements: There is no mention of what took place during the final "close-out" week (it may not belong here, however).

Analysis: the logistic regression approach is reasonably clear, i.e., stepwise selection and (presumably) backward elimination to remove parameters with $p<0.05$. However, the choice of $p<0.05$ should be more clearly justified - what is the impact of eliminated parameters on the coefficients of those retained (i.e., is there evidence of confounding and does confounding increase when these terms are eliminated)?

Results

Study participants: response/participation rates (which are remarkably good) should be presented.

Potential predictors of adoption of THS: Adoption of THS by men and women differed by nearly 30% but was not statistically significant. Should this be presented as "no influence of sex"?

Discussion

How might the statistically significant reduced adoption of THS among heavier smokers and among non-Latino smokers be interpreted? Did these groups increase their conventional cigarette use or simply fail to adopt THS as much as other groups? Might the results suggest that these smokers are more habituated or committed to smoking conventional cigarettes?

It seems intuitive that adoption of THS would be preferentially higher among those who found it easy to use and more enjoyable. Is there any alternative interpretation? Similarly, might study participants selecting both THS types reflect populations more interested in variety than single product loyalty? How might these observations be used to predict what might happen in the US if THS were broadly available to current conventional cigarette smokers? Can some quantitative range of projection(s) be made regarding what proportion of cigarette smokers might adopt THS, i.e., quit conventional cigarette smoking?

I noticed that the two study locations in a US state (i.e., NC) where tobacco is an important crop – and cigarettes are produced – were the least likely to adopt THS. This is interesting and might be explored further.

Japanese studies demonstrated higher rates of THS adoption among smokers intending to quit smoking combusted cigarettes. In contrast, this study demonstrated higher adoption of THS among those who never attempted to quit. How might this be explained? What are the characteristics of smokers not intending to quit but adopting THS (vs. those not adopting, or those intending to quit)?

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: I have no competing interests. Intermittently (ending in early 2018), I provided Philip Morris (sponsor of this study) epidemiological consulting support on study design and interpretation, unrelated to the current study and manuscript.

Reviewer Expertise: Epidemiology with a primary focus on concepts and methods as used to evaluate occupational, environmental and consumer product exposures.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have

significant reservations, as outlined above.

Author Response 20 Jun 2021

Christelle Chrea, Philip Morris Products S.A., Neuchatel, Switzerland

General comments

○ **Discussion – General comments**

Several parts of the Discussion section have been reworked to address the Reviewers comments on the Discussion.
In particular, the Reviewer commented that, while important insights were generated regarding the group of adult smokers who volunteered for the study, no inference can be drawn with regard to non-tobacco users or users of other nicotine-containing products. We have reflected this comment in the Discussion as follows: "The sample was not representative of the U.S. current adult smoker population, which should be considered when interpreting the results."
Regarding the need for post-market studies, we outline in the Discussion that objectives of such research is to provide actual levels of THS adoption and use patterns once THS is commercially marketed in a given market (in the context of this manuscript, in the U.S.) and what are the drivers of adoption in the population.

Specific comments

○ **Abstract**

The Abstract has been slightly edited according to the Reviewer's comments on its content and structure, with no alteration to the message presented (i.e. removed repetitious sentences, as well as addition, restructuration and move of sentences to a different part of the abstract for clarity, etc...).
As also recommended by the Reviewer, the overall text of the manuscript has been further edited to correct any grammatical errors and further improve the flow.

○ **Introduction**

As suggested by the Reviewer, the Introduction was edited to present how other regulatory authorities are considering different types of products, including e-cigarettes, and to provide examples of the MRTPs available in the U.S. (including MRTP applications accepted for review).
We also updated in the Introduction the status of the PMI MRTP Applications for *IQOS* to indicate that, in July 2020, the FDA authorized the following claim "AVAILABLE EVIDENCE TO DATE: The IQOS system heats tobacco but does not burn it. This significantly reduces the production of harmful and potentially harmful chemicals. Scientific studies have shown that switching completely from conventional cigarettes to the *IQOS* system significantly reduces your body's exposure to harmful or potentially harmful chemicals.", together with the appropriate citation. In addition, we specified that "As of March 31, 2021 *IQOS* was available in 66 countries."

○ **Methods**

The Methods section was edited to outline why the study locations were chosen ("The study locations were chosen to recruit a sufficiently large and diverse number of current U.S. adult

daily smokers. In each city, C&C Market Research was operating a dedicated booth within a mall, which was used as study site.").

A citation has been added to reference "Good Epidemiological Practice" (Hoffmann, 2019), and this study characteristic remains indicated under Setting sub-section of the Methods, along with the information related to the Institutional Review Board.

THS description has been moved under Introduction section as suggested.

Regarding the final "close-out" week, the Data collection and measurements sub-section of the Methods has been edited as follows: "During the "close-out" week period participants were not required to record any data, however, they were able to call the toll-free telephone hotline for the continued surveillance of potential adverse events (AEs)."

For the logistic regression described under Analysis sub-section of the Methods, we think that there is a misunderstanding. The backwards elimination was performed with a criteria p<0.05 as a selection threshold to retain the variable in the model, not to remove it. In addition, it was tested if the model could be improved using this procedure.

○ **Results**

The Reviewer recommended to present the response/participation rates. The aim of this analysis was to assess the potential predictors of adoption of the Tobacco Heating System (THS) by current U.S. adult smokers after six weeks of THS product use. With this in mind, the response/participation rates are, therefore, of limited value. This being said, the response/participations rates can be found as part of the full study report, which is publicly available as part of Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications and can be accessed through the following link: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications.

Regarding potential predictors of adoption of THS, the Reviewer suggested that, because our results showed that "Adoption of THS by men and women differed by nearly 30% but was not statistically significant," it should be indicated as "no influence of sex". We agree with this comment and we confirm that the Results section include the following wording: "No influence of sex was found" (after Figure 2).

○ **Discussion – Specific comments**

The Reviewer requested how the statistically significant reduced adoption of THS among heavier smokers and among non-Latino smokers could be interpreted. Indeed, heavy current adult smokers might need more time to adopt THS than current adult smokers smoking fewer cigarettes per day. Actually, based on the literature, Latino smokers tend to consume fewer cigarettes per day than non-Latino smokers. Therefore, the results of non-Latino smokers in our sample are likely related to the findings on heavy smokers who have a reduced adoption of THS.

The Reviewer asked whether some quantitative range of projection(s) could be made regarding what proportion of cigarette smokers might adopt THS. We think that a quantitative projection would go beyond the objective of the study and would be difficult to justify.

The Reviewer noticed that the two study locations in a U.S. state (i.e., NC) where tobacco is an important crop – and cigarettes are produced – were the least likely to adopt THS, and suggested to further explore this aspect. The study locations (eight cities spread across the

U.S.) were chosen to recruit a sufficiently large and diverse number of U.S. adult daily smokers. The study was aimed at assessing differences by demographic characteristics and smoking habits rather than by study location.

The Reviewer asked our perspective on Japanese studies data, which reported higher rates of THS adoption among current adult smokers intending to quit smoking combusted cigarettes, compared to our study, which, in contrast, demonstrated higher adoption of THS among those who never attempted to quit. Comparing the data from Japan and the U.S. is difficult, because we would compare pre-market data (U.S. data) with post-market data (Japan data) and different cultural environment. When it comes to the characteristics of the current adult smokers not intending to quit but adopting THS, we would not expect a difference in profile.

Competing Interests: No competing interests were disclosed.

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