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How do Risk Perceptions Drive Smokers to Completely Switch to a Smoke-Free Tobacco Product (*IQOS*™)? A Four-Country Cohort Study*

by

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SUMMARY

Background: The perceived reduced formation of harmful chemicals (RF) or perceived reduced risk of harm (RH) of a smoke-free tobacco product relative to combustible tobacco products may influence its acceptance and use patterns among adult smokers and therefore impact public health. We analyzed whether and how the RF and/or RH of the heated tobacco product (HTP) *IQOS*™ impacted "exclusive" (100%) *IQOS*™ use in Japan, Italy, Germany, and Russia.
Methods: Between 2016 and 2020, adult participants from longitudinal *IQOS*™ user cohorts in Japan (*N* = 6257), Italy (*N* = 8137), Germany (*N* = 8474), and Russia (*N* = 7231) repeatedly indicated the reasons for using *IQOS*™, including reasons referring to RF and RH, during their first 48 weeks in the cohort. Logistic and Cox regression were used to analyze the relationships between RF and/or RH indications for using *IQOS*™ and exclusive or stable exclusive *IQOS*™ use.
Results: At week 48, exclusive *IQOS*™ use in Japan (odds ratio [OR] = 1.89), Italy (OR = 3.35), Germany (OR = 3.48), and Russia (OR = 3.05) was more likely among participants who more frequently (highest *vs.* lowest category of number of RF and/or RH indications) indicated RF and/or RH as a reason for using *IQOS*™. In Japan, where other HTPs were also marketed, this was also true for the overall HTP category. Also, in Japan where RF and RH could be indicated separately as reasons for using *IQOS*™, indicating RH (OR = 2.92) compared to RF (OR = 1.81) resulted in a greater likelihood of exclusive *IQOS*™ use within the highest category of RF or RH indications. In Japan (hazard ratio [HR] = 0.74), Italy (HR = 0.80), Germany (HR = 0.72), and Russia (HR = 0.85), *IQOS*™ users who indicated RF and/or RH as a reason for using *IQOS*™ had a lower risk of becoming a stable non-exclusive than stable exclusive *IQOS*™ user as well as a 10–25% lower number of weeks until reaching stable exclusive *IQOS*™ use.
Conclusions: Perceived reduced formation of harmful chemicals (RF) or perceived reduced risk of harm (RH) of *IQOS*™ have a significant impact on *IQOS*™ users' switching to exclusive *IQOS*™ use and the acceleration of stable exclusive *IQOS*™ use. This may also be true for the overall HTP category. Moreover, perceived RH of *IQOS*™ seems to be a stronger driver for exclusive *IQOS*™ use than perceived RF. [Contrib. Tob. Nicotine Res. 32 (2023) 50–64]

KEYWORDS

Perceived reduced harm; *IQOS*™; heated tobacco product (HTP); smoke-free; complete switching

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ZUSAMMENFASSUNG

Hintergrund: Die wahrgenommene reduzierte Bildung schädlicher chemischer Verbindungen (RB) oder das wahrgenommene reduzierte Schadensrisiko (RS) eines rauchfreien Tabakprodukts im Vergleich zu brennbaren Tabakprodukten kann seine Akzeptanz und sein Konsumverhalten bei erwachsenen Rauchern und damit die öffentliche Gesundheit beeinflussen. Wir haben analysiert, ob und wie die RB und/oder das RS des Tabakerhitzer-Produktes (HTP) *IQOS*™ die „exklusive" (100 % *IQOS*™) Verwendung des Produktes in Japan, Italien, Deutschland, und Russland beeinflussen.

Methoden: Zwischen 2016 und 2020 gaben erwachsene Teilnehmer aus Längsschnitt-Kohorten von *IQOS*™ Nutzern in Japan (N = 6257), Italien (N = 8137), Deutschland (N = 8474) und Russland (N = 7231) während ihrer ersten 48 Wochen in der Kohorte wiederholt ihre Gründe für die Verwendung von *IQOS*™ an, einschließlich der Gründe, die sich auf RB und RS beziehen. Logistische und Cox-Regression wurden verwendet, um die Beziehungen zwischen den RB- und/oder RS-Angaben für die Verwendung von *IQOS*™ und exklusiver oder dauerhaft exklusiver *IQOS*™-Verwendung zu analysieren.

Ergebnisse: In Woche 48 war die exklusive Verwendung von *IQOS*™ in Japan (Odds Ratio [OR] = 1,89), Italien (OR = 3,35), Deutschland (OR = 3,48) und Russland (OR = 3,05) wahrscheinlicher bei Teilnehmern, die häufiger (höchste *vs*. niedrigste Kategorie der Anzahl von RB- und/oder RS-Angaben) RB und/oder RS als Grund für die Verwendung von *IQOS*™ angaben. In Japan, wo auch andere HTP vermarktet wurden, galt dies auch für die gesamte HTP-Kategorie. Ebenfalls in Japan, wo RB und RS separat als Gründe für die Verwendung von *IQOS*™ angegeben werden konnten, führte die Angabe von RS (OR = 2,92) im Vergleich zu RB (OR = 1,81) innerhalb der höchsten Kategorie der RB- oder RS-Angaben zu einer größeren Wahrscheinlichkeit der exklusiven Verwendung von *IQOS*™. In Japan (Hazard Ratio [HR] = 0,74), Italien (HR = 0,80), Deutschland (HR = 0,72) und Russland (HR = 0,85) hatten *IQOS*™-Nutzer, die RB und/oder RS als Grund für die Verwendung von *IQOS*™ angegeben hatten, ein geringeres Risiko, ein dauerhaft nicht-exklusiver anstatt dauerhaft exklusiver *IQOS*™-Nutzer zu werden, sowie eine um 10–25 % geringere Anzahl von Wochen bis zum Erreichen einer dauerhaft exklusiven *IQOS*™-Verwendung.

Schlussfolgerungen: Die wahrgenommene reduzierte Bildung schädlicher chemischer Verbindungen (RB) oder das wahrgenommene reduzierte Schadensrisiko (RS) von *IQOS*™ haben einen signifikanten Einfluss auf die Umstellung der *IQOS*™-Nutzer zur exklusiven *IQOS*™-Verwendung und die Beschleunigung einer dauerhaft exklusiven *IQOS*™-Verwendung. Dies scheint auch für die gesamte HTP-Kategorie zu gelten. Darüber hinaus scheint das RS von *IQOS*™ ein stärkerer Antriebsfaktor für die exklusive Verwendung von *IQOS*™ zu sein als die RB. [Contrib. Tob. Nicotine Res. 32 (2023) 50–64]

RESUME

Contexte: La perception d'une formation réduite de constituants chimiques nocifs (RF) ou la perception du risque réduit de nocivité (RN) des produits du tabac sans fumée par rapport aux produits du tabac brûlé peut influencer l'acceptation et l'utilisation des produits du tabac sans fumée chez les fumeurs adultes et donc avoir un impact sur la santé publique. Nous avons analysé si et comment RF et/ou RN du produit du tabac chauffé (HTP) *IQOS*™ impactent l'utilisation «exclusive» (100%) d'*IQOS*™ au Japon, en Italie, en Allemagne, et en Russie.

Méthodes: Entre 2016 et 2020, les participants adultes des cohortes longitudinales d'utilisateurs d'*IQOS*™ au Japon (N = 6257), en Italie (N = 8137), en Allemagne (N = 8474) et en Russie (N = 7231) ont indiqué à plusieurs reprises leurs raisons d'utilisation d'*IQOS*™, y compris les raisons faisant référence à RF et RN, au cours de leurs 48 premières semaines dans la cohorte. La régression logistique et la régression de Cox ont été utilisées pour analyser les relations entre les mentions de RF et/ou RN comme raisons d'utilisation d'*IQOS*™ et l'utilisation exclusive d'*IQOS*™ ou l'utilisation stable et exclusive d'*IQOS*™.

Résultats: En semaine 48, l'utilisation exclusive d'*IQOS*™ au Japon (odds ratio [OR] = 1,89), en Italie (OR = 3,35), en Allemagne (OR = 3,48), et en Russie (OR = 3,05) était plus élevée, pour la catégorie la plus élevée par rapport à la catégorie la plus basse, chez les participants qui ont indiqué plus fréquemment RF et/ou RN comme raisons d'utilisation d'*IQOS*™. Cela était également vrai au Japon, où d'autres HTP sont commercialisés, pour la catégorie HTP en général. De plus, au Japon, où RF et RN pouvaient être indiqués séparément, indiquer RN (OR = 2,92) par rapport à RF (OR = 1,81), dans la catégorie la plus élevée de mentions, entraînait une plus grande utilisation exclusive d'*IQOS*™. Au Japon (hazard ratio [HR] = 0,74), en Italie (HR = 0,80), en Allemagne (HR = 0,72) et en Russie (HR = 0,85), les utilisateurs d'*IQOS*™ qui ont indiqué RF et/ou RH comme raisons d'utilisation d'*IQOS*™ avaient un risque moindre de devenir un utilisateur d'*IQOS*™ stable non exclusif que stable et exclusif ainsi qu'une réduction de 10 à 25 % du nombre de semaines avant d'atteindre une utilisation stable et exclusive d'*IQOS*™.

Conclusions: La perception d'une formation réduite de constituants chimiques nocifs (RF) ou la perception du risque réduit de nocivité (RN) d'*IQOS*™ ont un impact significatif sur la transition à une utilisation exclusive d'*IQOS*™ et sur la facilitation et l'accélération à une utilisation stable et exclusive d'*IQOS*™. Cela semble également être vrai pour la catégorie HTP en général. De plus, RN d'*IQOS*™ semble être un facteur plus important pour une utilisation exclusive d'*IQOS*™ que RF. [Contrib. Tob. Nicotine Res. 32 (2023) 50–64]

ABBREVIATIONS	
A-1, A-2, A-3	Analysis 1, Analysis 2, Analysis 3
ANOVA	Analysis of variance
CC	Manufactured and hand-rolled cigarettes
CI	Confidence interval
Cox	Cox proportional hazards regression analysis
HR	Hazard ratio
HTP	Heated tobacco product
ICC/ESOMAR	International Chamber of Commerce/ European Society for Opinion and Marketing Research
LAS	Legal age for smoking in a specific country
MRTP	Modified risk tobacco product
N/A	Not available
OR	Odds ratio
PATH	Population Assessment of Tobacco and Health
PMI	Philip Morris International
RF	Perceived reduced formation of harmful chemicals
RH	Perceived reduced risk of harm
SD	Standard deviation
TP	Tobacco product
US FDA	United States Food and Drug Administration

INTRODUCTION

Substitution of combustible tobacco products (TP) with less harmful smoke-free (i.e., non-combustible) TP alternatives is an important public health strategy of tobacco harm reduction, with complete (i.e., 100%) substitution being more effective in reducing individual and population harm than only partial substitution (1–4). To achieve this, smoke-free TPs must be accepted and adopted by adult smokers who otherwise would continue to smoke so they can completely switch from combustible to smoke-free TPs (2–3). It is therefore important to identify the major sociodemographic (5–6) and motivational factors that drive acceptance of and complete switching to smoke-free TPs, in order to inform research and tobacco control policies on strategies to increase the number of smokers who completely switch to smoke-free TPs, which will reduce overall population harm (7–8). The motivations and reasons why adult smokers switch – or do not – from combustible to less harmful smoke-free TPs differ (5–6, 9–10) and may vary from country to country (10–11). Motivations to switch to smoke-free TPs include similarity with combustible TPs (9, 12); sensory properties and nicotine delivery (7, 12–13); satisfaction (7, 9); enjoyment (9, 14), convenience (7); appraisal of new technologies (9); absence of smoke, reduced smell, and cleanliness (9, 15); social acceptability (9, 14); and intentions to reduce or quit smoking altogether (6–7, 9, 12–13, 15–16); but also prevailing health conditions (6), and notably the perceived risk of harm of TPs (7, 9, 14, 17–22). Indeed, accurate, truthful and non-misleading scientific communication on the reduced risk profile of smoke-free TPs, such as the reduced exposure and reduced risk claims authorized by the United States Food and Drug Administration (US FDA) in the modified risk TP (MRTP) order (23–27), may facilitate adult smokers' switching from combustible to smoke-free TPs (1, 7, 9, 28).

To date, however, there is limited information on whether and how the perceived risk of harm of a smoke-free TP impacts switching to smoke-free TP use (17–18, 29–30). One study investigated the impact of perceived harm on complete switching to "exclusive" (i.e., 100%) use of a smoke-free TP (18). The authors found that among adult dual users of cigarettes and e-cigarettes who participated in the U.S. Population Assessment of Tobacco and Health (PATH) study, those who perceived e-cigarettes as less harmful than cigarettes appeared more likely to switch to exclusive e-cigarette use (18). However, to our knowledge no other study has investigated the impact of perceived risk of harm on future use of heated tobacco products (HTP), and in particular, on exclusive use of HTPs.

HTPs, including the HTP *IQOS*™, are a category of smoke-free TPs that heat tobacco but do not burn it and therefore have the potential to present considerably less risk of harm than combustible TPs (12). As a consequence, smokers who completely switch to *IQOS*™ or other scientifically substantiated HTPs are exposed to much lower levels of harmful chemicals than those who continue smoking cigarettes (23, 31–34). Moreover, HTPs contain tobacco and therefore provide smokers a similar experience (e.g., sensory properties, nicotine delivery profile, and ritual) to that of smoking a cigarette (12–13), thus positioning HTPs as acceptable alternatives to cigarettes.

In the present prospective longitudinal study, we investigated whether and how the perceived reduced formation of harmful chemicals (RF) or the perceived reduced risk of harm (RH) of the HTP *IQOS*™ impacted *IQOS*™ use patterns – in particular "exclusive" *IQOS*™ use and "stable exclusive" *IQOS*™ use – among *IQOS*™ user consumer cohorts in the four culturally and socioeconomically different countries Japan, Italy, Germany, and Russia.

METHODS

Participants and design

Participants were adults, who were at least 1 year older than the legal age for buying TPs in their respective countries and were current users of *IQOS*™, from Philip Morris International (PMI)'s prospective, longitudinal, open, and online *IQOS*™ user cohorts in Japan (N = 6257; ≥ 21 y), Italy (N = 8137; ≥ 19 y), Germany (N = 8474; ≥ 19 y), and Russia (N = 7231; ≥ 19 y). The cohorts were managed by an independent global research company. Participants were randomly selected within strata of sex and age (legal smoking age [+1 year]–29, 30–39, 40–49, 50+) from country-specific nationwide *IQOS*™ user databases (reference populations) on the basis of inclusion and exclusion criteria (Supplementary Figure S1). Inclusion criteria consisted of agreement to participate in the *IQOS*™ user consumer cohort, being of country-specific legal smoking age +1 year, ownership of an *IQOS*™ device, use at recruitment of ≥ 3 tobacco units per day (including cigarettes and tobacco sticks/units used with *IQOS*™ or other HTPs), and at the time of recruitment having bought their *IQOS*™ device within the past 4 weeks (to ensure capturing all changes and transitions in TP use behavior among *IQOS*™ users who had just started using *IQOS*™).

Exclusion criteria consisted of employment in market research or having a family member working for a tobacco manufacturer, employment in a legal profession, and being a pregnant or breastfeeding woman.

All eligible participants received an e-mail invitation to participate in the study. Upon accepting the invitation to participate, participants were presented with a consent form, which included information about the aim of the study, study participation duration, the voluntary nature of their participation, confidentiality, use of data, and data privacy. All individuals who provided electronic informed consent to the study were included in the survey and were sent regular e-mail invitations to complete the follow-up study questionnaires. All cohort participants who completed a questionnaire received an e-mail voucher of appreciation valued at about 10 USD depending on the country. The study was conducted in accordance with the International Chamber of Commerce/European Society for Opinion and Marketing Research (ICC/ESOMAR) International Code on Market, Opinion and Social Research and Data Analytics, the ethical principles that have their origin in the Declaration of Helsinki, and Good Epidemiological Practice. The present analysis is based on data that were collected from eligible participants who were followed up between 2016 and 2020 during their first 48 weeks in the cohort.

Data collection and measures

- *Perceived reduced relative harm*

RF and RH were defined as the attributes of the HTP *IQOS*™ as perceived by the *IQOS*™ users (i.e., based on their opinion of the product's RF and RH properties). As part of repeated (weekly in the first 12 weeks, subsequently monthly) follow-up online questionnaires, participants were asked to select from a list of multiple reasons why they were using *IQOS*™ (17–29 reasons depending on the country) or not using *IQOS*™ (26–29 reasons depending on the country). The reasons concerning RF or RH were all phrased as RF or RH statements for *IQOS*™ in comparison to cigarettes. Depending on the country, the statements referred to either RF or RH only, or both RF and RH (Table 1). Therefore, all analyses (except the separate analyses of RF and RH in Japan) were conducted using "RF and/or RH" as the predictor variable (i.e., indicating any of RF only, RH only, or both RF and RH as a reason for using *IQOS*™ in any week of the follow-up was regarded as a single indication).

- *Current TP use status*

As part of the repeated online questionnaires, participants were also asked to provide information on their current TP use, defined as TP use in the last 7 days. The 100 cigarettes lifetime criterion (35) or other lifetime criteria for TP use were not used to define current use. Participants were classified as "exclusive" users of a particular TP or TP category (e.g., HTP category) if they reported using that TP or the TP category for 100% of their total TP consumption in the last 7 days. A "stable" *IQOS*™ user was defined as a TP user being at least in the last 4 weeks of the 48-week follow-up a "stable exclusive" (100% *IQOS*™), "stable situational" (> 0 but < 100% *IQOS*™), or "stable abandoner" (0% *IQOS*™) *IQOS*™ user.

Table 1. RF and RH statements that could be indicated by participants as reasons for using *IQOS*™ by country [1].

Japan	Two reasons referred to RF (the top 2) and two reasons to RH (the bottom 2)
	● *The tobacco vapor of IQOS has significantly less harmful chemicals than the smoke of conventional cigarettes, but using IOQS is not risk free.*
	● *Has a significantly lower level of harmful chemicals in its vapor than conventional cigarettes.*
	● *Because switching completely to IQOS is likely to present less risk of harm than continuing to smoke cigarettes (this does not mean IQOS is risk-free).*
	● *Because switching completely to IQOS is a better choice than continuing to smoke 1-mg cigarettes (this does not mean IQOS is risk-free).*
Italy and Russia	One reason referred to RF
	● *The levels of harmful chemicals in IQOS vapor are significantly reduced compared to a standard cigarette smoke.*
Germany	One reason referred to RF
	● *IQOS contains 90% less harmful chemicals: IQOS reduces the concentration of a representative set of chemicals which are identified as being harmful in tobacco smoke on average by 90% in comparison to a cigarette.*

Besides the reasons for using *IQOS*™ that referred to RF or RH, depending on the country, participants could also select multiple other reasons out of lists for (i) using *IQOS*™ (29 [Japan], 17 [Italy], 21 [Germany], or 25 [Russia] other reasons) or (ii) not using *IQOS*™ (29 [Japan], 26 [Italy], 27 [Germany], or 28 [Russia] other reasons). Besides RF and RH, the two other main predictors of exclusive *IQOS*™ use across all 4 countries were (i) *IQOS*™ is different (i.e., more hygienic: no fire, no smoke, less smell, no odor and stains on hands, furniture) to smoking cigarettes and (ii) participants liked the (real tobacco) taste of *IQOS*™.

Abbreviations: RF: perceived reduced formation of harmful chemicals; RH: perceived reduced risk of harm.

[1] The statements on RF and RH were not consistent in the four countries because the information/wording of the statement ("claims") had to be phrased in accordance with the local regulations and law in the individual countries.

• *Demographics*

Participants were asked to provide sociodemographic information, including sex, age, education, living situation, employment status, and income as part of the recruitment questionnaire.

Statistical analysis

All statistical analyses were conducted by an independent statistics and research consulting company (Smartech s.r.l., Milano, Italy) using SPSS Statistics software for Windows (version 25; IBM Corp., Armonk, NY, USA). In all four countries, the cohort samples were randomly selected from the reference population (*IQOS*™ users in the country associated *IQOS*™ user database), ensuring the sample representativeness for the reference population and an equal distribution of possible confounding variables (including sociodemographic and other factors related to using *IQOS*™) among sample subgroups (i.e., exclusive or stable exclusive *IQOS*™ users). For these reasons, and due to (i) the high collinearity among some of the socioeconomic and sociodemographic variables and (ii) an additional confirmatory sensitivity analysis, adjustment for possible confounding variables was not performed. Except for the indications of RF or RH, the last observation carried forward imputation method was used in cases where participants did not provide information on TP use in a specific week or month. Statistical significance was set at $P < 0.05$; and reported P values are two-sided.

Demographic characteristics were compared using Chi-square tests, *z*-tests, *t*-tests, analyses of variance (ANOVAs), and the Bonferroni correction for multiple comparisons. A sequential three-step analysis (A-1 to A-3) approach was used to calculate effect sizes for different aspects of the impact of RF and/or RH on exclusive *IQOS*™ use: (A-1) whether and how strongly RF and/or RH (yes/no) impacts exclusive *IQOS*™ use, (A-2) whether and how strongly persistently RF and/or RH (number of indications of RF and/or RH during follow-up as an indicator for consistently indicating [having certainty about] RF and/or RH) impacts exclusive *IQOS*™ use in a dose–response manner, and (A-3) whether and how strongly RF and/or RH (yes/no) impact the stabilization of exclusive *IQOS*™ use.

Binary logistic regression was used to investigate A-1, the relationship between indicating (yes/no) RF and/or RH as a reason for using *IQOS*™ during follow-up and the likelihood (yes/no) of exclusive *IQOS*™ use at week 48. Binary logistic regression was also used to investigate A-2, the relationship between the number of indications of RF and/or RH (in five categories: 0, 1, 2–5, 6–10, 11–13 indications) during follow-up and the likelihood (yes/no) of exclusive *IQOS*™ use at week 48. In an additional sensitivity analysis, the same analyses were performed for longer periods of 60 and 72 weeks of follow-up. In Japan, where a number of other manufacturers' HTPs (e.g., Glo™ and Ploom™) were marketed at the time of the study, the same analyses were also performed for the overall HTP category (including *IQOS*™ and alternative HTPs). Moreover, in Japan, where *IQOS*™ users were able to indicate RF and RH individually as reasons for using *IQOS*™ in the follow-up questionnaires, the same analyses were performed separately for RF and RH.

Cox proportional hazards (Cox) regression analysis was used to investigate A-3, the relationship between indicating RF and/or RH (yes/no) as a reason for using *IQOS*™ during the 48-week follow-up and the risk (yes/no) of the hazard event of ending the 48-week period as a stable non-exclusive *IQOS*™ user (i.e., the categories of stable situational or stable abandoner *IQOS*™ user). Only stable *IQOS*™ users (i.e., stable exclusive, stable situational, or stable abandoner *IQOS*™ users) were included in this analysis. Besides the risk of becoming a stable non-exclusive *IQOS*™ user, we analyzed the percentage of *IQOS*™ users who became stable exclusive *IQOS*™ users and the time to reach the status of stable exclusive *IQOS*™ use. In an additional sensitivity analysis treating possible confounding variables, using stepwise forward regression, Cox models were adjusted for covariates that reached a significance level of $P < 0.10$ in the model. Candidate covariates included indicating (yes/no) taste or advantages in comparison with cigarettes (e.g., no smoke, no ash, less smell, less staining of curtains/furniture) as a reason for using *IQOS*™, as well as the socioeconomic and sociodemographic covariates of sex, age, education, living situation, employment status, and income. *IQOS*™ users who were missing any of these covariates were excluded from the sensitivity analysis. The unadjusted Cox models were considered the final models because in each country, (i) the cohort samples were randomly extracted from the reference populations, thereby ensuring equal distribution of confounding variables among sample subgroups, and importantly, (ii) the adjusted results did not differ statistically significantly and meaningfully from those of the unadjusted models.

RESULTS

Participant characteristics

The demographic characteristics of the *IQOS*™ users in Japan (N = 6257), Italy (N = 8137), Germany (N = 8474), and Russia (N = 7231) differed statistically significantly among the four countries (Table 2). However, the mean age and age range were similar (mean ± SD [range]; Japan, 46.6 ± 9.9 [21–85]; Italy, 42.7 ± 11.5 [19–85]; Germany, 43.8 ± 12.2 [19–85]; and Russia, 36.0 ± 9.5 [19–85]), and in all four countries the majority of participants were male (76%, 69%, 59%, and 67%, respectively). Most participants in the four cohorts were graduates from high school or college/university/graduate school, and the two most common living situations were "Family with children living at home" (Japan 39% and Italy 36%) and "Living with partner/spouse (no child)" (Germany 33% and Russia 30%). The most frequent employment status was "in employment" or "self-employed" among Japanese (80%), German (72%), and Russian (88%) participants (data for Italy not available), and the two most common income categories were in the middle-income range among Japanese (40%) and German (48%) participants (data for Italy not available), while they were in the low-income range (37%) among Russian participants.

Table 2. Baseline participant characteristics of *IQOS*™ user consumer cohort samples in Japan, Italy, Germany, and Russia.

	Number (*n*) and percentage (% [95% CI]) or mean (SD [range])				
	Japan (*N* = 6257)	Italy (*N* = 8173)	Germany (*N* = 8474)	Russia (*N* = 7231)	*P*
Sex (*n* [%])					
Male	4784 (76%)	5651 (69%)	4969 (59%)	4820 (67%)	< 0.0001
Female	1473 (24%)	2522 (31%)	3505 (41%)	2411 (33%)	
Age (*n* [%])					
LAS–29	284 (5%)	1382 (17%)	1191 (14%)	1978 (27%)	< 0.0001
30–39	1251 (20%)	2275 (28%)	2180 (26%)	3055 (42%)	
40–49	2268 (36%)	2493 (31%)	2052 (24%)	1528 (21%)	
50+	2454 (39%)	2023 (25%)	3051 (36%)	670 (9%)	
Mean (SD [range])	46.6 (9.9 [21–85])	42.7 (11.5 [19–85])	43.8 (12.2 [19–85])	36.0 (9.5 [19–85])	< 0.0001
Education[1] (*n* [%])					
Elementary School/Junior High School (1)	245 (4%)	683 (9%)	2409 (31%)	6 (0.1%)	< 0.0001
High School/Old Junior High School (2)	2161 (37%)	3344 (42%)	1202 (16%)	340 (5%)	
Junior College/Higher Professional School (3)	1138 (19%)	1376 (17%)	857 (11%)	1077 (15%)	
College/University/Graduate School (4)	2235 (38%)	2539 (32%)	2338 (30%)	5538 (79%)	
None of these (5)	73 (1%)	0 (0.0%)	960 (12%)	32 (0.5%)	
Living Situation (*n* [%])					
Living at home with parents	898 (15%)	1116 (14%)	304 (4%)	529 (8%)	< 0.0001
Living with friends/housemates	91 (2%)	159 (2%)	302 (4%)	220 (3%)	
Living by yourself	1019 (17%)	1043 (14%)	1503 (19%)	988 (15%)	
Living with partner/spouse (no child)	979 (17%)	1867 (24%)	2609 (33%)	1899 (30%)	
Single parent living with children	192 (3%)	267 (3%)	267 (3%)	166 (3%)	
Family with children living at home	2328 (39%)	2741 (36%)	2183 (28%)	1735 (27%)	
Empty nesters (children have left home)	272 (5%)	398 (5%)	785 (10%)	564 (9%)	
Others	117 (2%)	109 (32%)	175 (2%)	286 (4%)	
Employment status[2] (*n* [%])					
Housewife/Homemaker	294 (5%)	N/A	174 (2%)	224 (3%)	< 0.0001
Student/Apprentice	48 (1%)	N/A	533 (6%)	266 (4%)	
Retired/Pensioner	98 (2%)	N/A	347 (4%)	84 (1%)	
Unemployed	163 (3%)	N/A	79 (1%)	297 (4%)	
In employment/Self-employed	5017 (80%)	N/A	6123 (72%)	6360 (88%)	
Other income[3] (*n* [%])	637 (10%)	N/A	1218 (14%)	0 (0.0%)	
(1)	278 (7%)	N/A	240 (5%)	868 (19%)	N/A[4]
(2)	659 (17%)	N/A	982 (19%)	825 (18%)	
(3)	852 (22%)	N/A	1245 (25%)	701 (15%)	
(4)	710 (18%)	N/A	1163 (23%)	750 (16%)	
(5)	492 (13%)	N/A	598 (12%)	428 (9%)	
(6)	512 (13%)	N/A	834 (16%)	301 (6%)	
(7)	430 (11%)	N/A	–	795 (17%)	
RF and/or RH mentioned during follow-up (*n* [%])					
No	1,552 (24.8%)	5,032 (61.6%)[5]	1,827 (21.6%)	1,887 (26.1%)	< 0.0001
Yes	4705 (75.2%)	3141 (38.4%)	6647 (78.4%)	5344 (73.9%)	
Stable exclusive *IQOS*™ at week 48 (*n* [%])					
No	2978 (47.6%)	3358 (41.1%)	3406 (40.2%)	2605 (36.0%)	< 0.0001
Yes	3279 (52.4%)	4815 (58.9%)	5068 (59.8%)	4626 (64.0%)	

Participants of PMI's open online *IQOS*™ user consumer cohorts in Japan (≥21 y), Italy (≥19 y), Germany (≥19 y), and Russia (≥19 y) were randomly selected from PMI's country-specific *IQOS*™ user databases and were followed-up between 2016 and 2020 during their first 48 weeks in the cohort. Chi-square tests and ANOVA were used to test for statistical differences in categorical and continuous parameters among countries, and the Bonferroni correction for multiple comparisons was applied.

Abbreviations: LAS: legal age for smoking in country +1 year (i.e., Japan ≥ 21 y; Italy, Germany, and Russia ≥ 19 y); N/A: not available; PMI: Philip Morris International; RF: perceived reduced formation of harmful chemicals; RH: perceived reduced risk of harm; SD: standard deviation.

[1] Education categories (different category grouping than in Supplemental Table 1 due to harmonization of country-specific categories):
Japan: (1) Elementary School/Junior High School; (2) High School/Old Junior High School; (3) Junior College/Higher Professional School; (4) College/University Graduate School; (5) None of these
Italy: (1) Elementary School/Junior High School; (2) High school/Old Junior High School; (3) Junior College/Higher Professional School; (4) College/University/Graduate School; (5) None of these
Germany: (1) Primary Education/Secondary Education not completed/Secondary Education completed; (2) High School/University entrance; (3) Technical School with statements/Vocational School/Technical School/Supervisor; (4) University degree/Technical degree; (5) Another type of professional training/None of these

Russia: (1) Elementary Education; (2) Secondary Education (8–11 forms); (3) Vocational School or College; (4) Higher Education (University/Institute)/Academic Degree/Second Higher Education; (5) None of these

[2] Different employment status category grouping than in Supplemental Table 1 due to harmonization of country-specific categories.

[3] Income categories:
Japan: [Yen]: (1) ≤ 199,999; (2) 200,000–299,999; (3) 300,000–399,999; (4) 400,000–499,999; (5) 500,000–599,999; (6) 600,000–799,999; (7) ≥ 800,000
Italy: N/A
Germany: [Euro]: (1) < 1000; (2) 1000–2999; (3) 3000–3999; (4) 4000–4999; (5) ≥ 5000
Russia: [Ruble]: (1) ≤ 50,000; (2) 50,001–70,000; (3) 70,001–90,000; (4) 90,001–110,000; (5) 110,001–130,000; (6) 130,001–150,000; (7) > 150,000

[4] No *P* value available due to different number of income categories across countries that could not be meaningfully harmonized and statistically compared

[5] In Italy, for some of the participants RF was not available to be selected as a reason for using *IQOS*™ from the beginning of the follow-up.

When stratified by country (Supplementary Table S1), stable exclusive *IQOS*™ use status was positively associated with the following socioeconomic and sociodemographic covariates: female sex (all four countries), lower mean age (Japan, Italy), higher mean age (Russia), lower education (Italy), intermediate education (Russia), "family with children living at home" (Japan, Italy, Germany), "living with partner/spouse (no children)" (Italy), "single living with children" (Russia), housewife/homemaker (Japan, Russia), and low income (Russia).

Descriptive TP use patterns at week 48 of follow-up

The TP use patterns of *IQOS*™ users at week 48 of follow-up by number of RF and/or RH indications were similar across countries (Figure 1). Indicating RF and/or RH as reasons for using *IQOS*™ more often during the 48-week follow-up was associated with higher percentages of exclusive *IQOS*™ users at week 48.

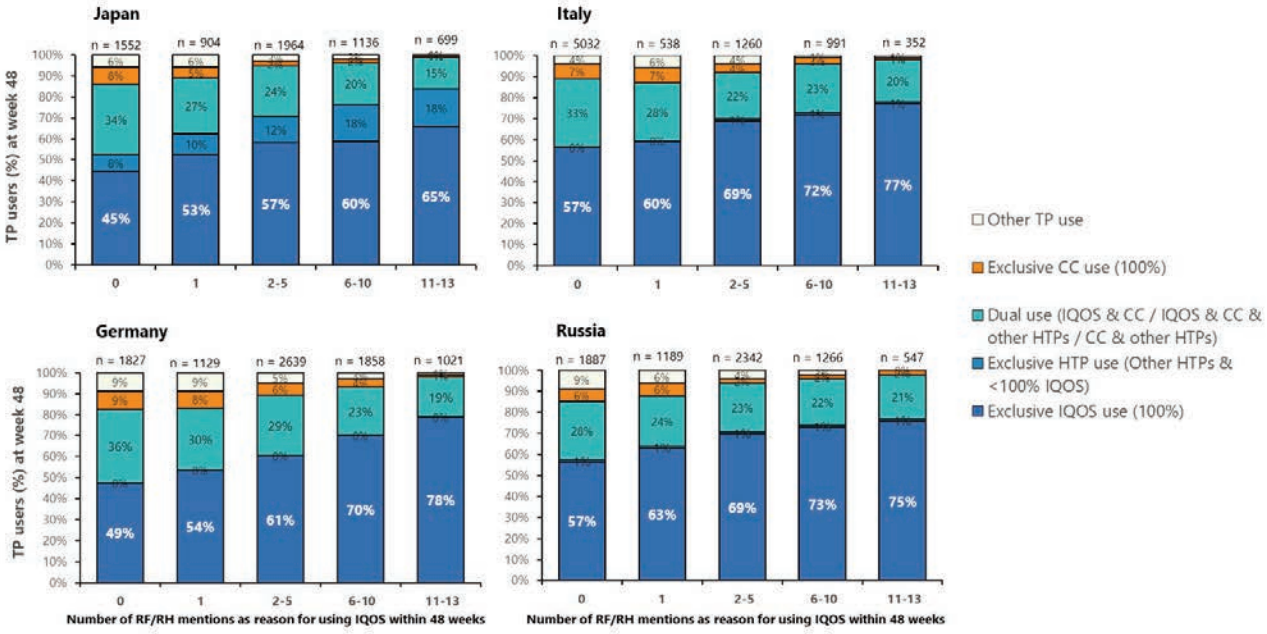

Figure 1. Patterns of TP use at week 48 by country and number of RF and/or RH indications. Participants of PMI's open online *IQOS*™ user consumer cohorts in Japan (*N* = 6257, ≥21 y), Italy (*N* = 8173, ≥19 y), Germany (*N* = 8474, ≥19 y), and Russia (*N* = 7231, ≥19 y) were followed-up between 2016 and 2020 during their first 48 weeks in the cohort.
Abbreviations: CC: manufactured and hand-rolled cigarettes; HTP: heated TP; Other TP use: participants with no TP use in the past 7 days and/or no intention to use TPs in future; PMI: Philip Morris International; RF: perceived reduced formation of harmful chemicals; RH: perceived reduced risk of harm; TP: tobacco product.

Table 3. Number of RF and/or RH indications and the likelihood of exclusive *IQOS*™ or HTP use.

Number of RF and/or RH indications	Japan (*N* = 6257)			Italy (*N* = 8173)		Germany (*N* = 8474)		Russia (*N* = 7231)	
	Exclusive HTP	Exclusive *IQOS*™		Exclusive *IQOS*™		Exclusive *IQOS*™		Exclusive *IQOS*™	
	OR (95% CI)	OR (95% CI)	(*n*)	OR (95% CI)	(*n*)	OR (95% CI)	(*n*)	OR (95% CI)	(*n*)
0	Reference (1.0)	Reference (1.0)	1552	Reference (1.0)	5032	Reference (1.0)	1827	Reference (1.0)	1887
1	1.65 (1.44–1.89)	1.12 (0.98–1.27) [1]	904	1.48 (1.25–1.76)	538	1.16 (1.03–1.31) [2]	1129	1.73 (1.54–1.95)	1189
2–5	2.28 (2.08–2.52)	1.35 (1.23–1.48)	1964	2.23 (1.98–2.51)	1260	1.59 (1.47–1.72)	2639	2.28 (2.08–2.49)	2342
6–10	3.38 (2.94–3.89)	1.47 (1.31–1.66)	1138	2.55 (2.22–2.93)	991	2.36 (2.14–2.61)	1858	2.74 (2.42–3.10)	1266
11–13	4.87 (4.00–5.94)	1.89 (1.62–2.21)	699	3.35 (2.61–4.29)	352	3.48 (3.00–4.03)	1021	3.05 (2.51–3.71)	547

Data are the OR (95% CI) for the relationship ($P < 0.0001$ if not indicated otherwise by a superscript) between the number of RF and/or RH indications by participants within the first 48 weeks of follow-up and the likelihood of exclusive HTP and/or *IQOS*™ use at week 48 in Japan (≥ 21 y), Italy (≥ 19 y), Germany (≥ 19 y), and Russia (≥ 19 y). Four groups of *IQOS*™ users - categorized by the number of times they indicated RF and/or RH as a reason for using *IQOS*™ over time - were compared to a reference group of *IQOS*™ users who did not make any indication of RF and/or RH. Indicating any combination of the two RF and/or RH related reasons for using *IQOS*™ in any week of the follow-up was regarded as a single indication.
Abbreviations: CI: confidence interval; HTP: heated tobacco product; OR: odds ratio; RF: perceived reduced formation of harmful chemicals; RH: perceived reduced risk of harm.
[1] $P = 0.096$; [2] $P = 0.011$

RF and/or RH indications and the likelihood of exclusive IQOS™ use

In all four countries, indicating RF and/or RH as a reason for using *IQOS*™ during follow-up was positively related to the likelihood of exclusive *IQOS*™ use at week 48 (A-1). Depending on the country, *IQOS*™ users who indicated RF and/or RH as a reason for using *IQOS*™ were 1.4–2.3 times more likely to report being exclusive *IQOS*™ users at week 48 than those who did not indicate RF and/or RH (odds ratio (OR) [95% confidence interval (CI)]: Japan, 1.39 [1.32–1.48]; Italy, 2.25 [2.08–2.43]; Germany, 1.86 [1.77–1.96]; and Russia, 2.29 [2.16–2.43]). The additional sensitivity analysis for 60 and 72 weeks of follow-up revealed similar ORs to those in the 48-week follow-up. Moreover, in all four countries, the number of times *IQOS*™ users indicated RF and/or RH as a reason for using *IQOS*™ during follow-up was positively related to the likelihood of exclusive *IQOS*™ use at week 48 (A-2; Table 3). Comparing the category with the highest frequency (11–13 indications) of RF and/or RH indications to the lowest frequency (0 indications), exclusive *IQOS*™ use at week 48 was 1.9–3.5 times more likely in the highest compared to the lowest category, depending on the country (Table 3).

RF and/or RH indications and the likelihood of exclusive HTP use in Japan

In Japan, where other HTPs (e.g., Glo™ and Ploom™) were also marketed at the time of the follow-up, indicating RF and/or RH as a reason for using *IQOS*™ during follow-up was also positively related to the likelihood of overall exclusive HTP use (*IQOS*™ and other HTPs) at week 48 (A-1). HTP users who indicated RF and/or RH as a reason for using *IQOS*™ were 2.6 times (OR = 2.57 [95% CI: 2.41–2.74]) more likely to be exclusive HTP users. Furthermore, the number of times HTP users indicated RF and/or RH as a reason for using *IQOS*™ during follow-up was positively related to the likelihood of exclusive HTP use at week 48 (A-2; Table 3). Compared to HTP users who did not indicate (0 indications) RF and/or RH as a reason for using *IQOS*™, HTP users who indicated RF and/or RH 11–13 times were 4.9 times more likely to be exclusive HTP users at week 48 (Table 3).

RF versus RH indications and the likelihood of exclusive IQOS™ use in Japan

In Japan, where *IQOS*™ users could indicate RF or RH separately as reasons for using *IQOS*™ during follow-up, indicating RF or otherwise RH during follow-up was both positively related to the likelihood of exclusive *IQOS*™ use at week 48 (A-1). The relationship for RH (OR = 1.48 [95% CI: 1.39–1.58]), however, was stronger than that for RF (OR = 1.40 [95% CI: 1.31–1.49]). Also, for both RF and RH, the number of times *IQOS*™ users indicated RF, or otherwise indicated RH, as a reason for using *IQOS*™ during follow-up was positively related to the likelihood of exclusive *IQOS*™ use at week 48 (A-2; Table 4). However, within the highest category (11–13 indications), indicating RH (OR = 2.92) increased the likelihood of exclusive *IQOS*™ use about 1.6 times more strongly than indicating RF (OR = 1.81) (Table 4).

Indicating RF and/or RH and the risk of becoming a stable non-exclusive IQOS™ user

In the Cox regression analysis (A-3), the risk of becoming a stable non-exclusive *IQOS*™ user (i.e., becoming a stable situational *IQOS*™ user or stable abandoner *IQOS*™ user) was in all four countries lower among *IQOS*™ users who indicated RF and/or RH compared to those who did not indicate RF and/or RH as a reason for using *IQOS*™ during follow-up (Table 5). This, in turn, also means that *IQOS*™ users who indicated RF and/or RH as a reason for using *IQOS*™ had a higher likelihood of becoming stable exclusive *IQOS*™ users. Depending on the country, the risk of becoming a stable non-exclusive *IQOS*™ user (hazard ratio (HR) = 0.74–0.85) was 1.2–1.4 times (i.e., 15%–26%) lower among those who indicated RF and/or RH as a reason

Table 4. Number of RF *vs.* RH indications and the likelihood of exclusive *IQOS*™ use in Japan.

Number of RF and/or RH indications	RF indications (n = 4170)		RH indications (n = 3894)	
	OR (95% CI)	(n)	OR (95% CI)	(n)
0	Reference (1.0)	1391	Reference (1.0)	1471
1	1.15 (1.02–1.30) [1]	693	1.34 (1.18–1.51)	667
2–5	1.41 (1.28–1.54)	1230	1.41 (1.27–1.55)	988
6–10	1.57 (1.37–1.79)	613	1.47 (1.28–1.68)	556
11–13	1.81 (1.46–2.24)	243	2.92 (2.29–3.72)	212

Data are ORs (95% CI) for the relationship (P < 0.0001 if not indicated otherwise by a superscript) between the number of RF or number of RH indications (indications were not mutually exclusive, therefore, models were mutually adjusted for RF and RH) by the participants (≥ 21 y) within the first 48 weeks of follow-up and the likelihood of exclusive *IQOS*™ use at week 48 in Japan. Four groups of *IQOS*™ users categorized by the number of times they indicated either RF or RH as a reason for using *IQOS*™ over time were compared to a reference group of *IQOS*™ users who did not make any indication of RF or RH. Indicating any combination of the RF-related reasons for using *IQOS*™ in any week of the follow-up was regarded as a single indication, and likewise for RH indications.
Abbreviations: CI: confidence interval; OR: odds ratio; RF: perceived reduced formation of harmful chemicals; RH: perceived reduced risk of harm.
[1] P = 0.026

for using *IQOS*™. The results of the covariate-adjusted Cox regression analysis (sensitivity analysis) were very similar to those of the unadjusted analysis (Table 5).
In all four countries, > 96% of stable exclusive *IQOS*™ users were already stable exclusive *IQOS*™ users before the last 4 weeks of follow-up. Depending on the country, the percentage of *IQOS*™ users who became stable exclusive *IQOS*™ users by week 48 of follow-up was 8–22% higher among those who indicated RF and/or RH as a reason for using *IQOS*™ during follow-up compared to those who did not (Table 5). Finally, in all four countries, the mean number of weeks until reaching stable exclusive *IQOS*™ use during follow-up was 10–25% lower among *IQOS*™ users who indicated RF and/or RH as a reason for using *IQOS*™ during follow-up compared to those who did not (Table 5).

Table 5. RF and/or RH indications, risk of stable non-exclusive *IQOS*™ use, percentage of stable exclusive *IQOS*™ users, and time to stable exclusive *IQOS*™ use.

	Indicating *vs.* not indicating RF and/or RH as a reason for using *IQOS*™ during 48 weeks of follow-up									
	Risk [1] of becoming a stable non-exclusive *IQOS*™ user				Percentage of stable exclusive *IQOS*™ users [2] until week 48			Mean number of weeks to stable exclusive *IQOS*™ use		
	Unadjusted analysis		Adjusted analysis [3]		Unadjusted analysis			Unadjusted analysis		
Country	HR (95% CI)	P	HR (95% CI)	P	Indicating % (95% CI)	Not indicating % (95% CI)	P	Indicating mean (95% CI)	Not indicating mean (95% CI)	P
Japan (N = 4557)	0.74 (0.69–0.79)	< 0.0001	0.74 (0.69–0.80)	< 0.0001	61% (59%–63%)	46% (43%–50%)	< 0.05	28.5 (27.5–29.0)	32.2 (31.1–33.4)	< 0.05
Italy (N = 6945)	0.80 (0.76–0.84)	< 0.0001	0.80 (0.76–0.84)	< 0.0001	70% (68%–73%)	55% (53%–56%)	< 0.05	20.1 (18.9–21.2)	26.9 (25.2–27.6)	< 0.05
Germany (N = 6437)	0.82 (0.77–0.88)	< 0.0001	0.83 (0.76–0.90)	< 0.0001	69% (76%–70%)	47% (44%–50%)	< 0.05	22.5 (21.8–23.2)	30.0 (28.8–31.2)	< 0.05
Russia (N = 5866)	0.85 (0.81–0.91)	< 0.0001	0.84 (0.78–0.90)	< 0.0001	70% (68%–71%)	62% (59%–64%)	< 0.05	22.7 (22.0–23.5)	25.3 (24.2–26.4)	< 0.05

Data are (i) unadjusted and adjusted HR (95% CI) based on Cox regression analysis for the relationship (P < 0.0001) between indicating RF and/or RH (yes/no) as a reason for using *IQOS*™ within 48 weeks of follow-up and the risk of becoming a stable non-exclusive *IQOS*™ user (i.e., stable situational *IQOS*™ user or stable abandoner *IQOS*™ user); (ii) unadjusted percentages of *IQOS*™ users becoming stable exclusive *IQOS*™ users; and (iii) unadjusted average numbers of weeks to stable exclusive *IQOS*™ use in Japan (≥ 21 y), Italy (≥ 19 y), Germany (≥ 19 y), and Russia (≥ 19 y). Adjusted models were adjusted for indicating (yes/no) taste and advantages in comparison with cigarettes (e.g., no smoke, no ash, less smell, less staining of curtains/furniture) as a reason for using *IQOS*™, as well as for age, sex, marital status, living situation, employment, and occupational level if the covariates reached a significance level of at least P < 0.10 in the model. *IQOS*™ users who were missing one of the covariates were excluded from the analysis.
Abbreviations: CI: confidence interval; HR: hazard ratio; RF: perceived reduced formation of harmful chemicals; RH: perceived reduced risk of harm; stable *IQOS*™ user: participant who was at least the last 4 weeks of the 48 weeks of follow-up an (i) stable exclusive (100% *IQOS*™), (ii) stable situational (> 0 to < 100% *IQOS*™) or (iii) stable abandoner (0% *IQOS*™) *IQOS*™ user.
[1] Here the term "risk" refers to the HR of Cox regression analysis.
[2] In all four countries, > 96% of stable exclusive *IQOS*™ users were already stable exclusive *IQOS*™ users before the last 4 weeks of follow-up.
[3] Sample sizes for the covariate-adjusted analysis were as follows: Japan (N = 3710, ≥ 21 y), Italy (N = 6232, ≥ 19 y), Germany (N = 4721, ≥ 19 y), and Russia (N = 4396, ≥ 19 y).

DISCUSSION

The present study is the first to cross-culturally and longitudinally investigate whether and how the perceived reduced formation of harmful chemicals (RF) or perceived reduced risk of harm (RH) of a smoke-free HTP impacts its exclusive and stable exclusive use. In four culturally and socioeconomically different countries, *IQOS*™ users who indicated RF and/or RH as a reason for using *IQOS*™ during follow-up were more likely to (i) be exclusive *IQOS*™ users after about 1 year of follow-up, (ii) become stable exclusive *IQOS*™ users during follow-up, and (iii) become stable exclusive *IQOS*™ users more rapidly than those who did not indicate RF and/or RH as a reason for using *IQOS*™. Moreover, the data from Japan suggest that *IQOS*™ users who consistently perceived *IQOS*™ as an RH product over time, were more likely to become exclusive *IQOS*™ users than those who consistently perceived *IQOS*™ as an RF product. Finally, the Japanese data suggest that the relationships identified for *IQOS*™ are also true for the overall HTP category.

Despite the cultural and socioeconomic diversity of the countries where *IQOS*™ user samples for the present study were drawn, all four samples were similar regarding the mean age and age range. Also, in all countries most participants were male, had completed high school/university, and had active employment status, allowing for comparability of the study results across the countries. Moreover, the sex and age profiles of the randomly selected samples of *IQOS*™ users in the four countries are comparable to HTP users of nationally representative surveys. Taking Japan as an example, the sex and age profile of *IQOS*™ users in the present study (76% men and 61% in the 21–49 year age group) is similar to the sex and age profile of HTP users from the Japanese Ministry of Health 2019 National Health and Nutrition Survey (36) (77% male and 60% in the 20–49 year age group).

Using a sequential three-step analysis approach (A-1 to A-3), we calculated effect sizes for different aspects of RF and/or RH and exclusive *IQOS*™ use. Given the different nature of the three analyses, for all four countries the effect sizes of A-1 (OR: 1.39–2.29) were intermediate between those of A-2 (OR: 1.89–3.48) and A-3 (HR: 0.74–0.82, i.e., 1.2 to 1.4 times impact). The higher effect sizes of A-2, which show the impact that RF and/or RH may have on exclusive *IQOS*™ use, result from the comparison of the extreme (lowest versus highest) categories of the number of RF and/or RH indications during follow-up. Conversely, we observed lower effect sizes of the most advanced and stringent A-3, which also considered the time period the individual *IQOS*™ users were stable exclusive users. This is because in this analysis, *IQOS*™ users had not only to fulfill the criterion of being an exclusive *IQOS*™ user, but also the criterion of being a stable exclusive *IQOS*™ user. In Japan, where other HTPs (e.g., Glo™ and Ploom™) are also marketed, A-2 revealed that repeatedly indicating (having certainty about) RF and/or RH as a reason for using *IQOS*™ was very strongly (OR = 4.87) associated with an increase in the likelihood of exclusive HTP use by a factor of 4.9. This is much higher than the corresponding likelihood for exclusive *IQOS*™ use only (OR = 1.89) in Japan and may be explained by two factors acting together: (i) the inherent likelihood of exclusive *IQOS*™ use (i.e., use of *IQOS*™ brand only; all combined use of *IQOS*™ with other HTP brands and/or cigarettes, cigarette use only, or other TP use would result in non-exclusive *IQOS*™ use) was lower than that of exclusive HTP use (i.e., any HTP brand or HTP brand combination possible; only combined use with cigarettes, cigarette use only, or other TP use would result in non-exclusive HTP use); and (ii) HTP users of more than one HTP brand may have more certainty about the RF/RH of HTPs and therefore are more likely to indicate RF and/or RH as reason for using *IQOS*™/HTPs during follow-up more frequently. This suggests that across the entire HTP category, there is a very high potential for HTP users to completely switch from combustible TPs to exclusive HTP use, providing that they are certain about the RF or RH profile of HTPs. Moreover, in Japan, where *IQOS*™ users were able to indicate RF or RH individually as reasons for using *IQOS*™, A-2 revealed that consistently indicating (having certainty about) RH (OR = 2.92) had the potential to switch combustible TP users 1.6 times more effectively to exclusive *IQOS*™ use than consistently indicating (having certainty about) RF (OR = 1.81). These results illustrate how the degree of certainty of perceived harm reduction can influence TP use (37). They also reinforce the need for clear, credible, and balanced information (8, 17); education and knowledge (11, 38); and communication (11) on the RF and RH profiles of different TP categories as well as correction of misperceptions (8, 11, 30). Armed with accurate information, TP consumers can understand and have certainty about the relative risks of the various TPs and can make informed choices regarding their use (11). This is of particular importance because misperceptions such as that HTPs or e-cigarettes are equally or even more harmful than cigarettes are still widely prevalent (8, 30). Understanding public perceptions of TP harm is important to help regulators develop appropriate policies and regulations for TP use (30). Eventually, public understanding has to be aligned with the general conclusions of authoritative sources, i.e., that smoke-free TPs are generally less harmful than combustible TPs (29, 38). Moreover, public health messages should help consumers understand how their individual health risk would change if a smoke-free TP is used only partially or exclusively (39). Finally, in the present study, the results of A-3 revealed that perception of *IQOS*™' RF and/or RH increased the likelihood of stable exclusive *IQOS*™ use by up to 1.4-fold and shortened the time to reach stable exclusive *IQOS*™ use by up to 25%. This underlines the importance of RF and RH communication in facilitating and accelerating of complete switching to stable exclusive *IQOS*™ use, and probably also to overall stable HTP or other smoke-free TP use. Indeed, to achieve overall population harm reduction, switching to stable exclusive smoke-free TP use is the most important behavioral change among smokers who do not quit all TP use.

To our knowledge, only one other study investigated the impact of perceived reduced harm on subsequent exclusive smoke-free TP use. In this study, PERSOSKIE et *al.* (18) examined data from US adult dual users of cigarettes and e-cigarettes (n = 2211) collected from the nationally representative longitudinal PATH study. The 1-year follow-up (2014–2015) of this study revealed similar results for

perceived harm and subsequent e-cigarette use as those observed in the present study for *IQOS*™ or HTP use. The authors reported that dual users of cigarettes and e-cigarettes who perceived e-cigarettes as less harmful than cigarettes were more likely to become exclusive e-cigarette users 1 year later (OR = 2.9 [95% CI: 1.7–4.8]) (18). This OR of 2.9 is not directly comparable with the OR revealed in the present study because we measured perceived reduced e-cigarette harm as a yes/no predictor variable, whereas the logistic regression model used by PERSOSKIE et *al.* (18) compared a "less harmful" category *versus* a collapsed group of three categories consisting of "about the same", "more harmful", and "don't know". However, the OR of 2.9 is intermediate between the lower ORs (1.39–2.29) revealed in the present study in A-1 and the higher ORs (1.89–3.48) revealed in the present study in A-2, suggesting that the association between harm perception and subsequent exclusive use of e-cigarettes is similar to that of *IQOS*™ and the overall HTP category.

Two further studies (17, 29) also investigated the impact of perceptions of harm on future e-cigarette use. However, neither study differentiated between switching partially or completely to e-cigarette use. Similar to the study by PERSOSKIE et *al.* (18), an earlier UK study by BROSE et *al.* (17) longitudinally assessed a general population sample of British adult smokers and former smokers (n = 6165) with a 1-year follow-up (2012–2013) and reported that among those who had never used e-cigarettes, perceiving e-cigarettes as less harmful than cigarettes predicted subsequent e-cigarette use (OR = 1.39 [95% CI: 1.08–1.80]). Unlike PERSOSKIE et *al.* (18), this UK study did not assess switching from dual (e-cigarette and cigarette) to exclusive e-cigarette use, but switching from never e-cigarette to e-cigarette use. This might explain the lower OR of 1.39 compared to the OR of 2.9 reported by PERSOSKIE et *al.* (18), assuming that switching from never e-cigarette use to e-cigarette use is less likely than from dual e-cigarette use to exclusive e-cigarette use. Similarly, another study by ELTON-MARSHALL et *al.* (29) based on longitudinal data (26,446 US adults) from the PATH study with a 1-year follow-up (2014–2015) reported that among non-current (93.4%) and current (6.6%) users of e-cigarettes, perceiving e-cigarettes as less harmful than cigarettes predicted subsequent e-cigarette use (OR = 1.97 [95% CI: 1.74–2.22]). As with the study of BROSE et *al.* (OR = 1.39) (17), the lower effect size (OR = 1.97) compared to that of PERSOSKIE et *al.* (OR = 2.9) (18) might be because ELTON-MARSHALL et *al.* also did not assess switching from dual to exclusive e-cigarette use, but from primarily non-current to subsequent e-cigarette use.

Communication about the RF and RH profile of smoke-free TPs – particularly claims authorized by recognized health authorities such as the US FDA's MRTP order and related claims (23, 25–27) – have been shown to motivate smokers to switch from combustible to smoke-free TPs (1, 7, 9, 28). In the present study, the reasons ("claims") the participants could indicate why they were using *IQOS*™ (Table 1) were relative RF and RH messages, i.e., the RF or RH of using *IQOS*™ in comparison to smoking cigarettes. As opposed to absolute harm messages, relative messages have been shown to be more effective in reducing harm perceptions and increasing use intentions of smoke-free TPs among smokers (8). Similarly, relative harm perceptions seem to be more important to individuals' TP information-seeking behaviors (39) and are associated with smoking onset and cessation (37) as well as switching to smoke-free TPs (17–18, 29). This suggests that people consider the health risk of TP use in terms of relative harm (37), so that tobacco control policy, regulation, and the content of public health messages should be informed by relative harm perceptions (39). Depending on the country, in the present study the reasons that could be indicated for using *IQOS*™ included either both RF and RH reasons, or an RF or RH reason alone. Of those, the reasons related to RF were similar to the second claim (see authorized statement II below) of the authorized Reduced Exposure information that PMI was granted for *IQOS*™ as part of its MRTP marketing order by the US FDA in July 2020 (23). The authorized information includes the available evidence to date: "(I) The *IQOS*™ system heats tobacco but does not burn it; (II) this significantly reduces the production of harmful and potentially harmful chemicals; and (III) 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." Therefore, given the similarity of RF reasons used in the present study with the Reduced Exposure claim (II) authorized for *IQOS*™ by the US FDA and the consistent effect sizes and results revealed in the present study for the four countries with different cultural and socioeconomic background, it is likely that the impact of the authorized Reduced Exposure claim (II) on the *IQOS*™ use patterns in the US (or other countries where comparable RF claims have been or will be communicated) will be similar to those identified in the present study. Also, if RH claims for *IQOS*™ or other HTPs that are similar to the RH reasons used in the present study were communicated in the U.S. or any other country, the use patterns of *IQOS*™ or other HTPs could be expected to be similar to those observed for *IQOS*™ and HTPs in the present study.

Strengths and limitations

Major strengths of this study include the longitudinal study design allowing for cause-effect inference, the inclusion of participants over a period of 4 years (2016–2020), and the observation period of about 1 year follow-up. Stratified random selection of participants from the reference populations in each of the four countries ensured sample representativeness and equal distribution of confounding variables among subgroups. The large sample sizes ensured statistical power and accuracy of the results, and the standardized assessment across the four culturally and socioeconomically different countries enabled comparability and greater generalizability of the results. Additional strengths are the use of relative risk claims that reflect people's natural thinking about the health consequences of smoking and the three-step analysis that allowed investigation of different aspects of RF and/or RH and exclusive *IQOS*™ use.

Limitations of the present work include the fact that the study was not based on nationally representative samples; however, the sex and age profiles of the randomly selected samples of *IQOS*™ users in the four countries were comparable to HTP users of nationally representative surveys.

Moreover, the study may have suffered from sampling and selection biases, as well as biases typically associated with self-reported measures and response bias, such as recall or social desirability biases. Nevertheless, studies examining bias in self-reporting of TP use have not found meaningful evidence of bias (40–43). Finally, the availability of different RF and RH statements to be selected by the participants as reasons for using *IQOS*™ as well as the wording of the RF or RH statements were similar but not entirely consistent across the four countries. Also, for the participants it might have not been obvious that among the harm related statements they could select as reasons for using *IQOS*™, there was a difference between RF (perceived reduced formation of harmful chemicals) and RH (perceived reduced risk of harm). Therefore, the data on the differentiation between RF and RH has to be interpreted with caution.

CONCLUSIONS

The perceived reduced formation of harmful chemicals (RF) or perceived reduced risk of harm (RH) of *IQOS*™, especially when indicated with certainty, has a significant and meaningful impact on complete switching to exclusive *IQOS*™ use and the facilitation and acceleration of stable exclusive *IQOS*™ use. This also appears true for the overall HTP category. Moreover, RH of *IQOS*™ seems to be a stronger driver for complete switching to exclusive *IQOS*™ use than RF. Our findings suggest that perceptions of the harm of HTPs and possibly also of other smoke-free TPs play an important role in tobacco harm reduction because they facilitate and accelerate adult smokers' complete and permanent switching to less harmful smoke-free TPs.
With regard to public health, it is important to continuously monitor exclusive and stable exclusive smoke-free TP use in post-market settings and ensure that adult smokers have access to accurate relative risk information to facilitate their switching from combustible to smoke-free TPs. Continuous post-market monitoring can also help clarify the risk perceptions of TPs in both smoke-free TP users and the population as a whole.

ASSOCIATED CONTENT

SUPPLEMENTARY MATERIAL

The Supplementary material is available free of charge on the Publications website:

- Supplementary information Figure S1 (PDF)
  Participant flow chart. Description of the participant flow from the reference population to the analytical sample based on inclusion and exclusion criteria, missing information, and loss to follow-up.
- Supplementary information Table S1 (PDF)
  Descriptive data (percentages and mean values) of baseline study participant characteristics by stable exclusive *IQOS*™ use status for user cohort samples in Japan, Italy, Germany, and Russia.
- Supplementary information SPSS Datasets (PDF)
  Anonymized SPSS Datasets for Japan, Italy, Germany, and Russia including the respective data maps.

DECLARATIONS

Ethics approval and consent to participate

This market/consumer research follows the ICC/ESOMAR International Code on Market, Opinion and Social Research and Data Analytics. All participants provided informed consent to the study.

Consent For Publication

The data for this analysis are fully anonymized. Participants agreed that their data and the aggregated information can be shared.

Availability Of Data And Material

The underlying anonymized data of this research is available on the INTERVALS online platform (https://www.intervals.science/) to share and explore smoke-free products assessment data and results, along with mechanistic studies on smoking-related diseases: Full SPSS Datasets (Supplementary Data S1) including data maps are available in the Supplementary material.

Competing Interests

K.F., S.R., and P.M. are employees of Philip Morris International., A.S., and M.C. are employees of Smartech s.r.l., an independent statistics and research consulting company commissioned by Philip Morris International.

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Authors' Contributions

S.R. and P.M. led the initial ideation process; K.F., A.S., and M.C. conceptualized the statistical analysis; A.S. conducted and M.C. supervised the statistical analysis; K.F., S.R., and P.M. interpreted the data; K.F. drafted the manuscript and created figures and tables; S.R., P.M., A.S., and M.C. reviewed and revised the manuscript; all authors reviewed and approved the final manuscript.

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