Changes in Respiratory Function and Physical Capacity among Smokers after Switching to IQOS: One Year Follow-Up

Almaz Sharman* and Tursynbek Nurmagambetov

Academy of Preventive Medicine of Kazakhstan, 4 Mitin Street, Almaty, Republic of Kazakhstan

Abstract: ***Background***: Combustible cigarettes (CC) smoking is a common risk factor for chronic obstructive pulmonary disease (COPD), which is the fourth leading cause of death in Kazakhstan. Switching to "heat-not-burn" tobacco products (IQOS) has been shown to have less deleterious health effect compared to CC for those who cannot quit smoking. The goal of the study was to explore respiratory and physical effects of switching from CC to IQOS in a population of long-time smokers in Kazakhstan. ***Methods:*** Two cohorts of men and women aged between 40 and 59 residing in Almaty (a large two-million city of Kazakhstan) were recruited into two cohort of 801 CC smokers and 400 IQOS users and matched by gender, age, education, and smoking history. Analyses also included 627 CC smokers and 308 IQOS users who maintained their tobacco product use during the first year of observation. Spirometry measurements and the 6-minute walk test (6MWT) were performed as a part of the baseline and one-year comprehensive assessments. In addition to spirometry, clinical assessments included components of metabolic syndrome and anthropometry. For comparative analysis between two cohorts Student's t-test and Chi-squared tests were used. ***Results:*** We observed significantly better outcomes for IQOS users in most of CAT scores, spirometry outcomes, and in some metabolic syndrome components. Although changes in the results between the baseline and the one-year assessments show comparable results, smokers of CC often show significantly faster decline in the health status compared to IQOS. Specifically, the changes in CAT score and in spirometry FEV1 over FVC ratios were worsening at higher pace for CC smokers compared to IQOS users. ***Conclusions:*** After one year of observation IQOS users demonstrated better outcomes for most of CAT scores and in the ratio of FEV1 over FVC in comparison to CC smokers.

Keywords: COPD; Combustible Cigarettes; "Heat-Not-Burn" Tobacco Products; IQOS; Metabolic Syndrome; Respiratory function.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in Kazakhstan. It is the third leading cause of death globally with 3.2 million deaths worldwide in 2019 [1]. In Kazakhstan, about 1.4 million people expected to have COPD [2]. COPD negatively affects quality of life and it is a major healthcare burden [3]. This condition is the third leading cause of hospital readmission within 30 days of the Initial admission[4]. Cigarette smoking is the most common risk factor for COPD [5]. COPD is traditionally defined by airflow obstruction and includes emphysema, gas trapping, and chronic bronchitis [6]. Systemic effects (e.g., on heart and muscles) and associated comorbidities (heart failure, metabolic disorders, sleep apnea syndrome, and depression) may complicate the course of disease posing challenges to managing COPD [7-9].

The results of a recent cross-sectional study of COPD among three groups of men and women aged 40-59 who currently smoke cigarettes, do not smoke, and stopped smoking 1-5 years ago [10] demonstrated that based on CAT, a clinically useful tool shown to identify smokers at risk for COPD exacerbations [11], respiratory symptoms are common in current smokers who have spirometry test results within the normal range. The authors found that 42% of current smokers had COPD symptoms based on a CAT score of ≥10, a prevalence of symptoms that was far greater than among former smokers and those who never smoked (17% and 12.5%, respectively). In addition, smoking cessation significantly reduced functional exercise incapacity such as inability to walk 450 meters within 6 minutes in the 6-Minute Walk Test (6MWT); 11% among ex-smokers compared to 16.7 % among current smokers [10]. Their findings were consistent with previously published data, including studies that documented exacerbation-like events in smokers without airway obstruction [11,12].

Smoking cessation reduces the severity of respiratory symptoms and slows the mean rate of lung function decline but does not eliminate the risk of progressive lung disease [13]. The results of the cross-sectional study demonstrated negative association between smoking cessation and activity limitations and positive association between smoking of combustible cigarettes and evidence of airway disease. As compared to never-smokers, current and former smokers had elevations in all components of the CAT score: cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep, and energy. At the same time, those parameters were lower among those who stopped smoking 1-5 years ago compared to those who continued to smoke.

Tobacco products alternative to conventional cigarettes have come on the global market with claims of being "modified risk" tobacco products. These electronic devices heat the tobacco up to 350˚C by the IQOS device instead of burning, which is supposedly delivers fewer toxins than cigarette smoke. Results of a 3-month reduced-exposure study in Japan showed that a reduction in 15 biomarkers of exposure to 15 harmful and potentially harmful compounds for the smokers who switched to a heated tobacco product for the duration of the study approached the reduction in the same biomarkers for smokers who quit for the duration of the study [14]. Results of another study showed that electronic cigarettes (i.e., a battery-operated device that emits doses of vaporized nicotine) might improve COPD outcomes, including subjective respiratory outcomes as well as annual exacerbation rate [15].

*Address correspondence to this author at the Academy of Preventive Medicine of Kazakhstan, 4 Mitin Street, Almaty, Republic of Kazakhstan; Email: asharman@zdrav.kz; Tel: +7-777-111-4202

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The aim of this study was to analyze the outcomes of CAT, spirometry results prior- and post-administering bronchodilator, the 6MWT, components of metabolic syndrome (MetS) at the baseline and changes that occurred between the baseline and the one-year assessment mark in both CC smokers and IQOS users, and determine if there are differences in these outcomes between these two groups.

METHODS

Study Design

The design of the study was described in detail in a earlier published protocol [16]. The study cohorts individuals (men and women) aged 40-59 years with a minimum of 10 pack-year smoking history who switched to and predominantly use (≥ 70% of time) the heated tobacco product IQOS with HeatSticks (exposure group) or who are currently smoking combustible cigarettes with a minimum of 10 pack-year smoking history (control group). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) definition was used to describe COPD exacerbations as an acute worsening of respiratory symptoms that results in an additional therapy [17]. Once signs of exacerbations were identified, special efforts were made by the clinical investigators, coordinators, and the principal investigator to establish their severe (mild, moderate, or severe), and relevance to COPD.

Outcome Measures

COPD. According to the GOLD was defined as a post-bronchodilator ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) being less than 70% as indicated by spirometry testing [17].

Respiratory symptoms. The COPD Assessment Test (CAT) is a quick and useful tool to weigh impact of COPD symptoms on health-related quality of life. Participants with a CAT score of 10 and more are considered having more severe respiratory symptoms [11].

MetS. We used the International Diabetes Federation (IDF) definition. Specifically, subjects were considered to have MetS if they had central obesity (waist circumference) > 94 cm in males and >80 cm in females for Euripides; >90 cm in males and >80 cm in females for Asians) plus two or more of the following criteria: (1) hypertriglyceridemia, ≥ 150 mg/dL; (2) reduced HDL cholesterol, < 40 mg/dL in males and < 50 mg/dL in females; (3) high blood pressure, ≥130/85 mm Hg; high fasting plasma glucose, ≥ 100 mg/dL.

Functional incapacity. The 6MWT determines functional exercise capacity in patients with moderate-to-severe heart or lung disease [18]. There are several reference systems predicting distance of 6MWT in healthy subjects. They take into account subject's gender, age, height and weight. No study has been conducted using this tool of functional capacity in Kazakhstan. We define the distance of 450 meters as a cut-off level for functional incapacity, as this value is highly correlated with maximal oxygen capacity [10].

Sample

This study was a matched-pair cohort study design where a pair contains one IQOS user and two conventional CC smokers were matched by gender, age, education, and baseline exposure level (number of pack-year). We recruited 400 participants in the exposure (IQOS) cohort and 801 participants in the control (CC) cohort: (1) IQOS (exposure group, N=400) and (2) CC smokers (control group, N=801; total sample size=1201).

To calculate the change in proportions with metabolic syndrome (MetS) we used a net change in the new number of the study participants with MetS in the one-year follow up assessment. If M0 is the number of cases with MetS and H0 is the number of cases without MetS at the baseline, and M1 and H1 are the same numbers for the year-one follow up assessment. New cases number with MetS in year one is M1 – M0. However, some H1 – H0 people with MetS at the baseline have become healthier and do not have MetS by the year one, which means the net change in MetS is equal to (M1 – M0) – (H1 – H0). By dividing this net change by the baseline number of people with MetS we also obtain percent change in the net cases by the year 1. We applied chi-squared method to test for significance of differences in the proportion with MetS between cigarette smokers and IQOS users. We applied similar approach to central obesity, hypertriglyceridemia, reduced HDL cholesterol, and high blood pressure outcomes.

Study Procedures

Spirometry. Spirometry data is collected using the combined spirometry system, BTL-08 SPIRO. All spirometry studies are reviewed centrally to ensure quality control. Bronchodilator responsiveness is considered positive if the subject had a ≥12% change in FEV1 or FVC above pre-bronchodilator measurements [19].

Each spirometer to be used in this study is tested and continuously standardized with a 3.0-liter syringe. Each clinical coordinator is certified after spirometry training. Quality assessments is made on each study.

Smokers are categorized for analysis using the GOLD staging system according to the results on spirometry, which is performed before and after two inhalations of salbutamol, 0.1 μg per inhalation. Among the criteria needed to make a diagnosis of COPD are deficits in the rate at which one can forcefully exhale. Most experts consider a low ratio (<0.70) of the FEV1 to the FVC after bronchodilator use to be a key diagnostic criterion [7].

Chronic Obstructive Pulmonary Disease Assessment Test (CAT). The CAT is a validated, short (8-item) questionnaire to be completed by study participants. Despite the fact that CAT is designed for patients with COPD, it can be used to measure respiratory symptoms among all participants including those who have preserved pulmonary function [10]. The CAT has a scoring range of 0-40, with the cut-off point equaling being equal to 10.

Anthropometry. Anthropometric measurements include height, weight, waist circumference, heart rate, blood pressure, and pulse oximetry.

The Six-Minute Walk Test. The 6MWT is a simple and effective test that measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. The KAPM clinic utilizes a 100-ft hallway to perform the 6MWT [18].

Laboratory Data. Blood donated by the study participants is processed at the KAPM COPD Center for shipment, analysis, and intermittent (at -20°C) and long-term (deep freeze at -80°C) storage in accordance with biobanking standards. The following assays are performed at a partner laboratory: CBC, blood cholesterol level, HDL, LDL, triglycerides; glucose, hemoglobin A1C; C-reactive protein; and fibrinogen.

Computer-Assisted Personal Interviewing. KAPM has developed an electronic data capture system in the form of its proprietary computer-assisted personal interviewing platform called ClouDoc. The questionnaire was designed to collect data on possible COPD risk factors including history of smoking, current smoking, level of smoking exposure (in pack-year), passive smoking, occupational and environmental hazards, including dusts, chemicals, and indoor fuel pollution. The questionnaire collects information on age, gender, ethnicity, education, occupation, and self-reported morbidity. It also includes questions on COPD exacerbations and on the use of CC, IQOS, electronic cigarettes, and other alternatives, as well as the dates of change for smoking preferences.

RESULTS

Basic demographic characteristics and smoking patterns of two study cohorts are summarized in Table 1. About half of the participants were women in both cohorts of cigarette smokers (49.6%) and IQOS users (49.3%). There were slightly more people under 50 years of age in each of the groups, 47.8% among cigarette smoker and 49.3% among IQOS users. The largest ethnicity were Kazakhs with over 60% in cigarette- and 55%in IQOS cohorts. From other ethnicities about a quarter were Russians comprising from 15% among cigarette smokers and 19% among IQOS users. Both groups were highly educated with around 84.5% people having higher education. The distribution of pack-years was similar in both cohorts with over 54% of people smoking more than 20 pack-years among cigarette smokers and over 57% among IQOS users; for the group using from 15 to 19 packs a year group those numbers were over 45% and about 43%, respectively.

Among IQOS users, more females (almost 93%) than males (88%) returned to participate in the one-year follow-up assessment, while for CC smokers those numbers were 93% for females and 91% for males (Table 2). By the follow-up assessment time, 18 (4.5%) of IQOS and 47 (5.9%) cigarette users quit smoking, 29 (7.25%) of IQOS users switched to cigarettes and 18 (2.25%) of cigarette smokers became IQOS users, and finally 38 (9.5%) from IQOS group and 62 (7.7%) from cigarette group left the study for various justified reasons. Overall, both groups had about the same retention rates: 81.7% for cigarette smokers and 81.2% for IQOS users.

COPD Assessment Test

At the baseline, CAT scores for all 8 questions were higher (significantly higher for cumulative and 5 questions on: cough, phlegm, chest tightness, being confident leaving home, and on the level of energy) for cigarette smokers compared to IQOS users (Table 3). At the one-year assessment, the scores for the first 4 questions were significantly higher for cigarette group. Cumulative CAT scores for cigarettes smokers were 12.84 (11.32) at the baseline (one-year) vs. 11.89 (10.53) for IQOS users, respectively, and these differences between two cohorts were highly significant ($p < 0.001$). By the one-year follow up time, those who used IQOS most of the time improved their cumulative CAT scores by 40% more than did cigarettes smokers, 0.13 vs. 0.09 (Figure 1).

Six-Minute Walk Test (6MWT)

There were significant differences between two types of smokers at the baseline for the 6MWT, however at the one-year assessment IQOS users showed significantly better results for the total distance (536.6m vs. 531.4m) and the average length of the laps (25.0 m vs. 24.5 m) (Table 3).

By the one-year assessment time improvement in the total distance were significantly better ($p < 0.05$) for IQOS cohort (-17.9m) compared to cigarette smokers (-9.6m). For the average number of laps walked, IQOS users did also significantly better (0.1laps vs. 1.5 laps for cigarettes cohort) with $p < 0.001$.

Spirometry Results

Spirometry results before and post administering bronchodilators are shown on Table 4. At the baseline there were no significant differences in FEV1 and FVC prior- or post bronchodilator between cohorts. At the one-year assessment all four respiratory measures, FEV1 and FVC before and post bronchodilator, show that IQOS users have significantly better outcomes than smokers of regular combustible cigarettes ($p < 0.05$). Within one year from the baseline to the one-year assessment time, all four spirometry measures and pre- and post-bronchodilator FEV1/FVC ratios on average improved better for IQOS compared to cigarette smokers. Moreover, post bronchodilator FEV1 and FVC outcomes' improvements were significantly better for IQOS vs. cigarette cohort (Figure 2).

Metabolic Syndrome and Related Health Examination Outcomes

At the baseline there were 249 (over 31%) people with metabolic syndrome among smokers of combustible cigarettes and 132 (33%) among IQOS users (Table 5). There were 522 (65%) cigarette smokers and 257 (64%) IQOS users with central obesity problem. At the baseline 281(35%) cigarette smokers and 156 (39%) IQOS users had triglycerides ≥ 150 mg/dL. There were 256 (32%) cigarette smokers and 113 (28%) IQOS users who had reduced HDL cholesterol level. And 257 (32%) participants from cigarette cohort and 110 (27%) had high blood pressure at the time of testing at the baseline. All these differences in proportions between two cohorts were not significant. The value of these health characteristics at

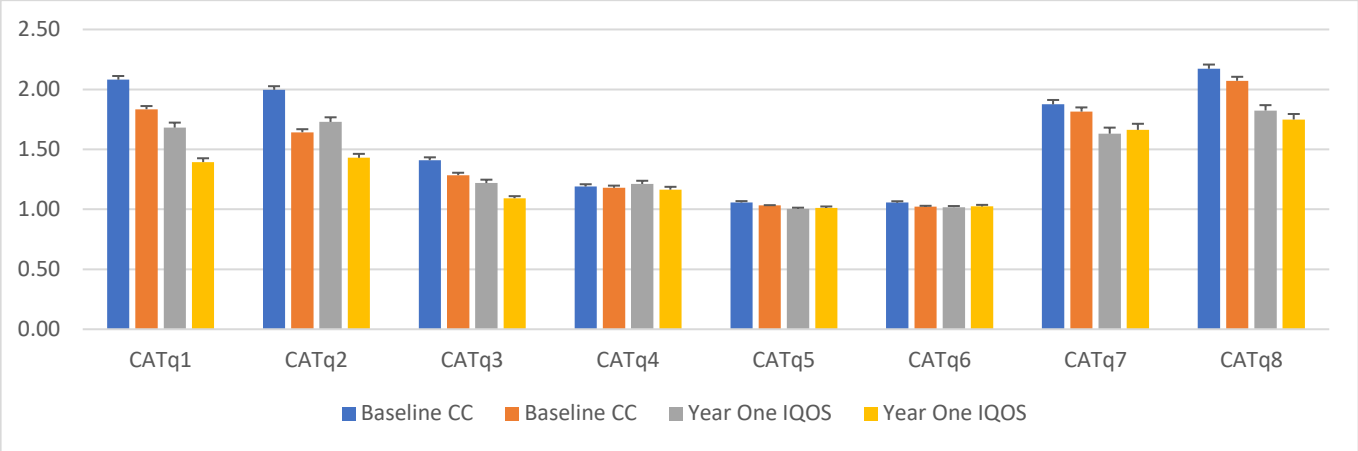

Figure 1: CAT scores at baseline (N=801) and year one (N=671) of CC and IQOS smokers.

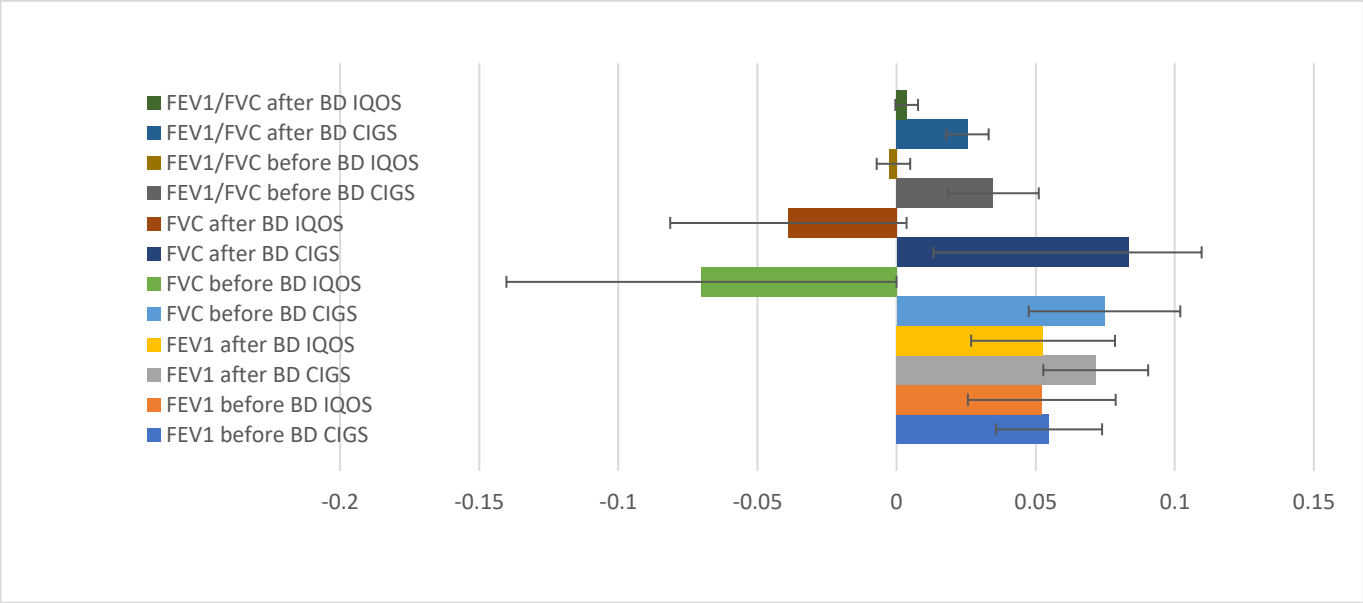

Figure 2: Changes in spirometry outcomes from the baseline to year one.

	Cigarettes smokers (N=801) N (%)	IQOS users (N=400) N (%)
Female	397 (49.6%)	197 (49.3%)
Age group		
<50	418 (52.2%)	203 (50.8%)
50+	383 (47.8%)	197 (49.3%
Ethnicity		
Kazakh	494 (61.7%)	220 (55.0%)
Russian	187 (23.4%)	104 (26.0%)
Other	120 (15.0%)	76 (19.0%)
Education		
Higher Education	677 (84.5%)	337 (84.4%)
Vocational Education	104 (13.0%)	51 (12.8%)
High School Diploma	20 (2.5%)	11 (2.8%)
Number of pack-year		
<10	0	0
10–19	363 (45.3%)	171 (42.6%)
20+	438 (54.7%)	230 (57.4%)

Table 1: Basic characteristics of participants by study groups of cigarette smokers and IQOS users.

Cohort	Gender	Participated at baseline	Participated at one-year follow-up (%)	Number of Quitted	Switched this type of smoking from other type	Stay with the same type of smoking (%)	Current Users (%)	Retention Rate
IQOS Users	Male	203	179 (88.2)	13	8	158 (77.8)	177 (87.2)	77.8%
	Female	197	183 (92.9)	5	9	169 (85.8)	179 (90.9)	85.8%
	Both	400	362 (90.5)	18	18	327 (81.2)	356 (89.0)	81.2%
Cigarette Smokers	Male	404	369 (91.3)	23	19	321 (79.5)	329 (81.4)	79.5%
	Female	397	370 (93.2)	24	8	333 (83.9)	342 (86.2)	83.9%
	Both	801	739 (62.3)	47	29	654 (81.7)	671 (83.8)	81.7%

Table 2: Distribution and retention of cigarette smokers and IQOS users from the baseline to the year-one assessment.

Indicators	CC Smokers		IQOS Users		Changes between Baseline and Year One[#]	
	Baseline N=801	Year One N=671	Baseline N=400	Year One N=362	CC Smokers (95% CI)	IQOS Users (95% CI)
CAT score, mean [SD]	12.84**[3.17]	11.32**[2.44]	11.89**[2.90]	10.52**[2.15]	0.09 (0.057 - 0.127)	0.13 (0.069 - 0.189)
6MWT, mean [SD], meter	520.8 [52.53]	531.4 [51.74]	520.0 [55.46]	536.6 [44.27]	-9.62*(-13.225 - -6.012)	-17.92*(-22.370 - -13.470)
6MWT, mean length of the lap [SD]	25.98 [0.40]	24.50**[1.94]	25.98 [0.44]	25.03**[1.72]	1.48**(1.331 - 1.637)	0.92**(0.727 - 1.118)
6MWT, mean number of laps [SD]	19.66 [2.02]	21.44 [2.54]	19.73 [2.57]	21.19 [2.31]	-1.74*(-1.938 - -1.548)	-1.45*(-1.754 - -1.153)

Notes: *(**) mean 95 (99) percent of significance level for comparison at either baseline or one-year assessments. In all cells the second row is the standard deviation. CAT = COPD (Chronic Obstructive Pulmonary Disease) Assessment Test. 6MWT = 6-Minute Walking Test.
Walking Test. Second line in the cells are 95% confidence interval.
[#] These last two columns are based on the subsample of participants who stayed in the study through the one-year follow up assessments and did not change their smoking preferences.

Table 3: Chronic Obstructive Pulmonary Disease Assessment Test (CAT) and the 6-Minte Walk Test (6MWT): comparison of the mean and standard deviation between cigarette smokers and IQOS users at baseline and one-year assessments.

Indicators	Cigarette smokers		IQOS Users	
	Baseline N=801	Year One N=671	Baseline N=400	Year One N=362
FEV1 before BD[#]	3.00(2.95 – 3.05)	2.94*(2.88 – 2.99)	3.07(3.00 – 3.13)	3.03*(2.96 – 3.10)
FEV1 after BD	3.11^(3.06 – 3.16)	3.02*(2.97 – 3.08)	3.17^(3.10 – 3.24)	3.11*(3.03 – 3.18)
FVC before BD	3.64(3.57 – 3.70)	3.55*(3.48 – 3.61)	3.59(3.51 – 3.67)	3.65*(3.57 – 3.74)
FVC after BD	3.74(3.67 – 3.80)	3.64*(3.57 – 3.70)	3.70(3.61 – 3.78)	3.72*(3.64 – 3.81)
FEV1/FVC before BD	0.83**(0.82 – 0.83)	0.83(0.825 – 0.833)	0.86**(0.85 – 0.88)	0.83(0.82 – 0.84)
FEV1/FVC after BD	0.835**(0.83 – 0.84)	0.83(0.829 – 0.837)	0.86**(0.856 – 0.87)	0.84(0.83 – 0.841)

Notes: All differences presented at either baseline or at year-one assessment between cigarette smokers or IQOS users. * Difference between cigarette and IQOS smokers is significant at 95% level. ** Difference between cigarette and IQOS smokers is significant at 99% level. [&] Difference between cigarette and IQOS smokers is significant at 90% level. ^ Difference between cigarette and IQOS smokers is significant at 90% level. [#] BD = bronchodilators.

Table 4: Difference in selected spirometry outcomes between cigarette smokers and IQOS users at the baseline and one-year assessment.

Indicator	Cigarette smokers		IQOS Users	
	Baseline N = 801	Year One N = 671	Baseline N=400	Year One N=362
Metabolic Syndrome	249 (31.1%) *	180 (27.6%)	132 (33.0%)	77 (23.0%)
Central Obesity	522 (65.0%)	378 (57.9%)	257 (64.3%)	173(51.6%)
Triglycerides ≥ 150 mg/dL	281 (35.1%)	230 (35.2%)	156 (39.0%)	111 (33.1%)
Reduced HDL Cholesterol	256 (32.0%)	108(16.5%)	113 (28.0 %)	35 (10.4%)
Blood pressure ≥ 130/85 mmHg	257 (32.1%)	202 (30.9%)	110 (27.5%)	74(22.1%)

Notes: * Percent of participants with the problem among cigarette smokers or IQOS users.

Table 5: Analysis of metabolic syndrome and selected blood chemistry results for cigarettes smokers and IQOS users at baseline and one-year assessment.

Indicators	CC Smokers	IQOS Users	Pearson Chi-Squared Probability
MetS	19 9.4%	31 29.3%	0.484
Central Obesity	46 10.7%	39 18.8%	0.068
Triglycerides≥150 mg/dL	-6 -2.6%	18 14.4%	0.221
Reduced HDL Cholesterol	101 47.7%	57 63.3%	0.19
Blood pressure ≥ 130/85 mmHg	0 0%	14 16.1%	0.007

Note: For significance of difference in the mean of change, Pearson Chi-squared test was used. First line is net change in the people with the problem described in the first column. Second line in the cells represents percent of increase for that outcome. For this table only participants who were on the same smoking status throughout the one-year assessment were considered.

Table 6: Changes in metabolic syndrome and selected blood chemistry results for cigarettes smokers and IQOS users at baseline and one-year assessment.

the one-year follow up were also measured and presented in Table 5.

Table 6 presents results of change in health outcomes from the baseline time to the year-one assessment. There was net decrease of 31 (29.3%) cases with MetS in the IQOS group compared to 19 (9.4%) in the cigarette group ($p = 0.484$). Another significant difference between two study cohorts was for central obesity with net decrease of 39 (18.8%) with this abnormality among IQOS users compared with net increase of 46 (10.7%) among cigarette smokers ($p = 0.068$); and for high blood pressure with net change of 0 for cigarette smokers group and with 14 (16.1%) for IQOS users group ($p = 0.007$).

DISCUSSION

To the best of our knowledge, this is the first longitudinal cohort observational study to demonstrate whether trends in the response variables across time differ between users of IQOS for at least 70% of the time and smokers of combustible cigarette for at least 70% of the time. The study follows two large matched cohorts of smokers of usual cigarettes and IQOS users for one year and it is being planned to follow these cohorts for another four years. Participants were examined at the baseline and at one-year follow up assessment for comprehensive list of health-related factors including demographic, respiratory, laboratory blood results, and behavioral characteristics. We used objective clinical and physical activity examination and responses to questionnaires to identify how the cohorts were similar or distinct at the baseline and one-year follow assessments and to track changes in main outcomes from the baseline to year-one follow up period.

While some results were mixed, we also observe significantly better outcomes for IQOS users in most of CAT scores, spirometry outcomes, and in some MetS components. Although changes in these outcomes between baseline and one-year assessment periods move towards similar negative results, smokers of usual cigarettes often show significantly faster decline in the health status. Specifically, the changes in CAT score and in spirometry FEV1 over FVC ratios were worsening at higher pace for cigarette smokers compared to IQOS users.

There were also some changes in the cohort size and smoking behavior during transition from the baseline assessment to the one-year follow assessment. The total number of participants reduced by 8 percent for various justifiable reasons. There were a few numbers of cigarette smokers who switched to using IQOS, and fewer IQOS users who went back to cigarettes by the one-year follow assessment and we excluded them from the analysis at the one-year follow up assessment.

For many important health outcomes, IQOS users have shown significantly healthier outcomes compared to cigarette smokers, for example, in four CAT components, cumulative CAT scores, and in post bronchodilator FEV1 and FVC results. Yet, for some other important outcomes, such as the 6-minute walk test, the results on differences were not significant. One of possible explanations can be that compared to much longer periods of smoking cigarettes, IQOS users have relatively much shorter experience with the new smoking device.

We hypothesized that IQOS may serve as a less risky alternative to combustible cigarettes and to other traditional tobacco products in a clinical setting. Specifically, we hypothesized that participants using IQOS will have less prevalent presence of respiratory symptoms, have better functional exercise capacity, and experience fewer exacerbations compared to those who smoke combustible cigarettes.

There are several limitations in this study. First, limitation is that this study is observational. Therefore, the study cannot produce definitive proof of a cause-effect relationship between the exposures and health outcomes, as with any observational medical research. Participants may leave the study for different reasons, which can compromise the validity of the study, particularly if the cohort dropout rates are different or the participants who remain in the study are different from those who drop out.

The results of this study demonstrate that participants who switched to IQOS have better outcomes in CAT scores, some spirometry and metabolic syndrome results compared to CC smokers. Further long-term research is needed into comparison between IQOS users and CC smokers. The results of this paper suggest that IQOS might be a better alternative for the people who cannot quit tobacco and who are concerned with smoking-related health outcomes.

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