

Respiratory Function and Physical Capacity in Combustible Cigarettes and Heated Tobacco Products Users: a Two-Year Follow-Up Cohort Study

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Abstract: *Background:* Cigarette smoking is the most common risk factor for chronic obstructive pulmonary disease (COPD), which is the fourth leading cause of death in Kazakhstan. Prior literature suggests that heated tobacco products (HTP) might be a better option for people who cannot quit smoking. The aim of this paper was to analyze the long-term effects of shifting to HTP use compared to continued combustible cigarettes (CC) use in long-term smokers.

Methods: A cohort of 1200 participants (400 HTP and 800 CC) aged 40-59 years with a minimum of 10 pack-year smoking history were recruited. The functional outcomes compared between HTP and CC users included: (1) COPD Assessment Test (CAT); (2) post-bronchodilator lung function; (3) 6-minute walking distance (6MWD) test; and (4) metabolic syndrome components. Multivariable linear mixed models were used to test associations between health outcomes and smoking type (HTP vs. CC) over time.

Results: After 24-month 188 (117 CC users and 71 HTP users) participants were lost to follow-up, while 107 (9%) participants quit smoking. The loss to follow-up was similar in both groups with 15% for CC users and 18% for HTP users. Linear mixed models showed HTP use was associated with lesser decrease in functional outcomes over time compared to CC users. Lung function decrease was significantly less in HTP users, while CAT scores, waist circumference, and systolic blood pressure were significantly better compared to CC users.

Conclusion: This study demonstrated that while both CC and HTP users experienced decrease in lung function, HTP users experienced it to a significantly lesser degree, while demonstrating better CAT score and physical characteristics compared to CC users. The results of this study suggest that HTP might be a less deleterious alternative compared to CC in people with long history of CC use and who cannot quit smoking.

Keywords: Cohort study, Combustible cigarettes, COPD self-reported score, Health outcomes, Heated tobacco products, Smoking.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death with 3.2 million deaths worldwide in 2019 [1]. COPD is the fourth leading cause of death and affects approximately 1.4 million people in Kazakhstan [2]. COPD is a major healthcare burden as it negatively affects the quality of life [3], and is the third leading cause of hospital readmission within 30 days [4].

Cigarette smoking is the most common risk factor for COPD [5]. 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 demonstrated that smoking significantly reduces functional exercise capacity such as ability to walk in the 6-Minute Walk Test (6MWD) [6]. Compared to never-smokers, current and former smokers had higher

values in all components of the COPD Assessment Test (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, these parameters were lower among those who stopped smoking 1-5 years ago compared to those who continued to smoke. However, smoking cessation is a challenge for long-term smokers. A recent study of 100 COPD patients showed that almost half of the patients continued smoking even after being diagnosed with COPD [7]. As a result, it is important to study less deleterious alternatives to CC use for those who cannot quit smoking.

Heated tobacco products (HTP) emerged on the global market as an alternative to combustible cigarettes (CC). HTP are presented as “modified risk” tobacco products because switching to HTP can potentially have less deleterious health effects associated with CC use. In a recent study, changes in a daily cigarette smoking, annualized disease exacerbations, lung function indices, patient-reported CAT scores, and 6-Minute Walk Test were measured in 19 COPD patients using HTP at 12-, 24-, and 36-

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months and compared with a group of age- and sex-matched COPD patients who continued using CC [8]. Subjects using HTP had a substantial decrease in annualized COPD exacerbations after three-year follow-up. In addition, substantial and clinically significant improvements in CAT scores and 6MWD were identified at all three time points in the HTP cohort. No significant changes were observed in COPD patients who continued smoking.

This paper reports the results of the previously described cohort study after two years of follow-up [9]. The aim of this paper was to analyze the functional outcomes of CAT, post-bronchodilator spirometry results, 6MWD test, and components of metabolic syndrome (MetS) over two-year follow-up time in long-term smokers who cannot quit. Another aim was to compare these functional outcomes between CC users and those who shifted to HTP use over time.

MATERIALS AND METHODS

Sample

This prospective cohort study was conducted in accordance with the principles and criteria set by the Declaration of Helsinki "On Ethical Principles for Medical Research Involving Human Subjects" and was approved by the Ethical Review Committee of the Academy of Preventive Medicine (protocol #4). Signed informed consent was obtained from all study participants before enrolment to the study.

The design of the study was described in detail in the previously published protocol [10]. Briefly, this study is a cohort study which matched one HTP user to two CC users by gender (men and women), age, education, and baseline exposure level (number of pack-years). HTP users were defined as participants who switched from CC to HTP use and predominantly use HTP during the day ($\geq 70\%$ of time). We recruited 1200 participants (400 HTP and 800 CC users) aged 40-59 years with a minimum of 10 pack-year smoking history. Study personnel provided participants information on health hazards associated with smoking and advised them on how to quit CC or HTP use. The participants were followed up for 24 months with functional outcomes and smoking status (HTP/CC/Quit smoking) measured at baseline, 12-, and 24-month period.

Functional Outcome Measures

The clinical and functional outcomes were compared between HTP and CC users and included

continuous: (1) patient-reported CAT scores; (2) post-bronchodilator lung function parameters, including forced expiratory flow in 1s – FEV1 and forced vital capacity – FVC; (3) exercise tolerance using 6MWD test; and (4) MetS components, including waist circumference, fasting glucose, blood lipids, and blood pressure.

Study Procedures

Computer-Assisted Personal Interviewing. Data was captured using ClouDoc a computer assisted personal Interviewing application. The questionnaire was designed to collect data on possible COPD risk factors including history of smoking, current smoking (HTP/CC/Quit smoking), level of smoking exposure (in pack-years), passive smoking, history of lung disease, etc., as well as personal independent variables, including age, gender, ethnicity, and self-reported morbidity.

Spirometry. Spirometry data was collected by a trained specialist 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 $\geq 12\%$ change in FEV1 or FVC above pre-bronchodilator measurements [11].

COPD self-reported score. The CAT is a validated, short (8-item) questionnaire to be completed by study participants [12]. CAT was designed for patients with COPD and can be used to measure respiratory symptoms among all participants including those who have preserved pulmonary function.

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

Exercise tolerance. 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 [12].

Laboratory Data. Blood donated by the study participants is processed at the KAPM COPD Center for shipment, biochemical analysis, intermittent (at -20°C) and long-term (at -80°C) storage in accordance with biobanking standards.

Statistical Analyses

Basic descriptive statistics used to characterize the study populations are presented as mean (SD) and

frequency (%). Demographic and personal characteristics were compared between HTP and CC users using the Student's t-test for continuous variables and Chi-Square test for categorical variables. One-way ANOVA was used to compare outcome measures at baseline, 12-, and 24- months for HTP and CC users separately. Outcomes which were significantly different between follow-up periods were further investigated using linear mixed models.

Linear mixed models including repeated measures were performed to compare the effects of smoking status on dependent variables: (1) patient-reported CAT scores; (2) post-bronchodilator lung function parameters, including FEV1 and FVC as separate outcomes; (3) exercise tolerance using 6-minute walking distance (6MWD) test; and (4) metabolic syndrome components, including waist circumference, fasting glucose, blood lipids, and blood pressure over time. These models included time (at baseline, 12-, and 24- months) and smoking status, and were further adjusted for participant's age, sex, years of smoking, ethnicity, history of lung disease, marital status, and interaction between time of follow-up and smoking

status as independent variables. Unstructured correlation matrix was used. Participants who quit smoking were excluded from repeated measures analyses. All statistical analyses were done with SAS (SAS Institute Inc., Cary, NC). A two-tailed *p* value of less than 0.05 was considered of statistical significance.

RESULTS

Recruited participants (N=1200) were followed-up for 24-months during which 16% of participants (188, 117 CC and 71 HTP users) were lost to follow-up. The loss to follow-up was similar in both groups with 15% for CC and 18% for HTP users. After 24-month of follow-up 107 (9%) participants quit smoking. The mean duration of HTP use was 7 months (SD 4). The demographic and clinical characteristics of the participants by baseline smoking status are presented in Table 1. There were no significant differences between CC and HTP users at baseline, except for CAT score, which was significantly lower for HTP group.

Table 1: Baseline Demographics of the Subjects on the Study Compared using Descriptive Statistics

	CC (n=800)	HTP (n=400)	P
Age (mean, SD)	49.16 (5.21)	48.95 (5.18)	0.5044 ^a
Ethnicity (n, %)			
Asian	592 (74.00%)	277 (69.25%)	0.0826 ^b
Caucasian	208 (26.00%)	123 (30.75%)	
Sex (n, %)			
Male	396 (49.50%)	196 (49.00%)	0.8703 ^b
Female	404 (50.50%)	204 (51.00%)	
Marital status (n, %)			
No	208 (26.00%)	111 (27.75%)	0.5177 ^b
Yes	592 (74.00%)	289 (72.25%)	
History of lung disease (n, %)			
No	749 (93.63%)	375 (93.75%)	0.9332 ^b
Yes	51 (6.38%)	25 (6.25%)	
Pack years (mean, SD)	22.83 (10.52)	22.77 (10.60)	0.8340 ^a
CAT score (mean, SD)	12.83 (3.17)	11.89 (2.89)	<.0001 ^a
FEV1 (mean, SD)	3.11 (0.74)	3.17 (0.71)	0.1616 ^a
FVC (mean, SD)	3.74 (0.88)	3.70 (0.83)	0.4392 ^a
6-Minute Walk Test (mean, SD)	510.89 (51.67)	509.86 (56.09)	0.7522 ^a
^a Student's t test			
^b Chi Square test			

The dynamic of the main outcomes between baseline, 12-, and 24-months follow-up are presented in Figure 1. Overall, both CC and HTP users experienced improvements in all health outcomes, except for measures post-bronchodilator lung function parameters. Both CC and HTP users experienced decline in lung function, but HTP users had better scores after 24-months of follow-up.

The differences between the main outcomes' values between baseline, 12-, and 24-month follow-up are presented in Table 2 separately for CC and HTP users. The analyses show that CAT score, FEV1, FVC, 6MWT, waist, HDL cholesterol, and systolic blood pressure (SBP) were significantly different between follow-up for CC and HTP users. In particular, CAT scores significantly decreased for both CC and HTP users, from 12.83 (SD 3.17) to 11.19 (SD 2.48) for CC users and from 11.89 (SD 2.89) to 10.68 (SD 2.32) for HTP users. Otherwise, the health parameters of the participants have improved over the observed period. The 6MWT increased from 510.89 (SD 51.67) to 525.64 (SD 47.74) for CC users and from 509.86 (SD 56.09) to 532.60 (SD 44.80) for HTP users (both $P < .0001$). Metabolic syndrome components including waist circumference, and HDL cholesterol significantly

improved over time, while HTP users also experienced decrease in systolic blood pressure (Table 2).

The results of repeated measures analyses of functional outcomes as dependent variables with smoking status (HTP vs CC) as main independent variable are presented in Table 3. Smoking type significantly was significantly associated with CAT scores, post-bronchodilator FVC, waist circumference for both CC and HTP users, while smoking type follow-up time interaction was associated with CAT score, FEV1, FVC, 6MWT, waist, and SBP.

The CAT scores have improved over time for both CC and HTP users (beta (12-month)=-0.0526, beta (24-months)=-0.0612, both $p < 0.0001$), though HTP smoking was significantly associated with lower CAT scores for 24-month follow-up compared to CC smokers (beta=0.0194, $p < 0.01$). Females had lower CAT scores compared to males (beta=-0.0133, $p < 0.05$), while having larger pack years, being Caucasian, and having previous history of lung disease increased the CAT score.

Post-bronchodilator FEV1 and FVC have decreased over time for both CC and HTP users. FVC for HTP users was significantly lower compared to CC users

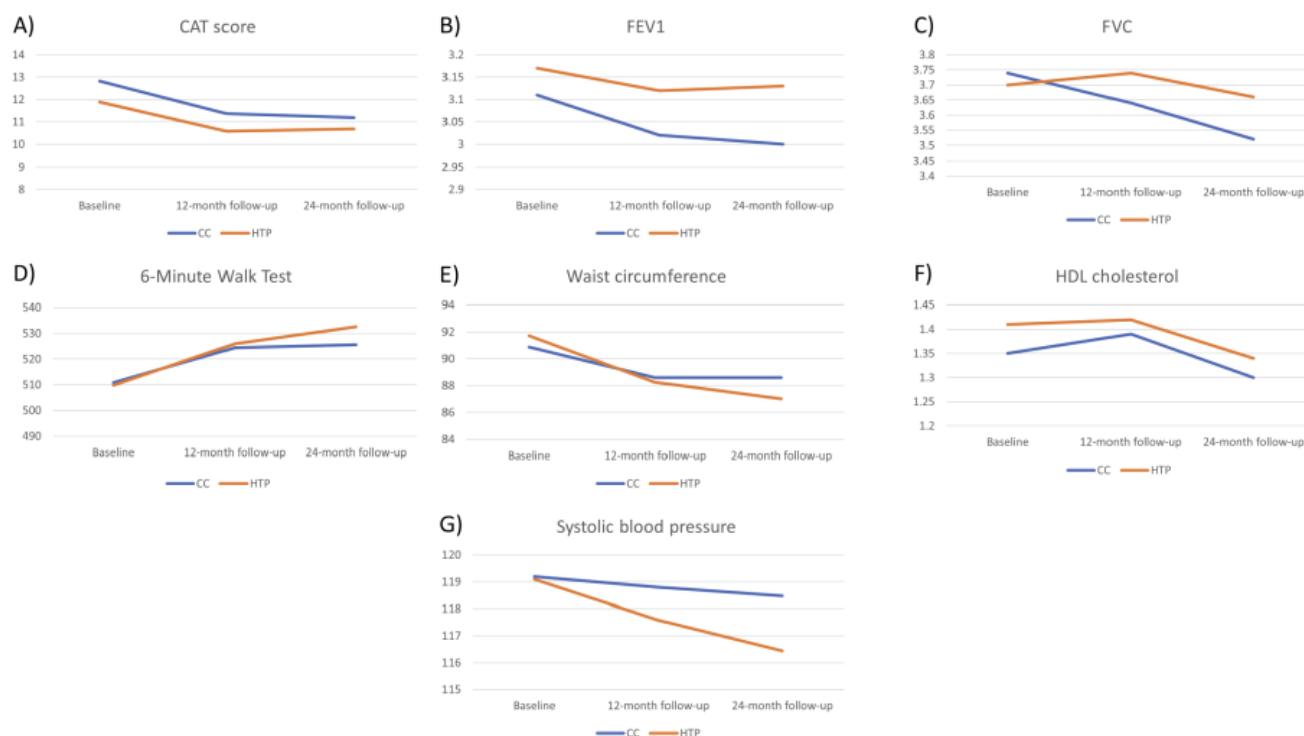


Figure 1: Change in the main functional outcomes over time at baseline, 12-, and 24-month follow-up visits for A) CAT score; B) FEV1; C) FVC; D) 6MWT; E) Waist circumference; F) HDL cholesterol; G) SBP.

Table 2: One-way ANOVA Comparison of CC and HTP Users at Baseline, 12-, and 24-Month Follow-up Visits

	Baseline	12-month follow-up	24-month follow-up	P ^a
CC	n=800	n=738	n=683	
CAT score (mean, SD)	12.83 (3.17)	11.37 (2.48)	11.19 (2.48)	<.0001
FEV1 (mean, SD)	3.11 (0.74)	3.02 (0.73)	3.00 (0.72)	0.0128
FVC (mean, SD)	3.74 (0.88)	3.64 (0.86)	3.52 (0.84)	<.0001
6-Minute Walk Test (mean, SD)	510.89 (51.67)	524.39 (47.37)	525.64 (47.74)	<.0001
Waist circumference (mean, SD)	90.89 (12.47)	88.60 (12.13)	88.59 (11.97)	0.0002
Fasting blood glucose (mean, SD)	5.32 (1.32)	5.45 (1.45)	5.37 (1.20)	0.1151
Triglycerides (mean, SD)	1.67 (1.15)	1.71 (1.38)	1.69 (1.28)	0.9695
HDL cholesterol (mean, SD)	1.35 (0.40)	1.39 (0.44)	1.30 (0.48)	<.0001
Systolic blood pressure (mean, SD)	119.19 (13.95)	118.80 (14.27)	118.48 (13.00)	0.6334
Diastolic blood pressure (mean, SD)	75.72 (10.42)	74.97 (10.32)	75.56 (8.99)	0.3369
HTP	n=400	n=362	n=329	
CAT score (mean, SD)	11.89 (2.89)	10.58 (2.21)	10.68 (2.32)	<.0001
FEV1 (mean, SD)	3.17 (0.71)	3.12 (0.67)	3.13 (0.68)	0.5187
FVC (mean, SD)	3.70 (0.83)	3.74 (0.80)	3.66 (0.80)	0.4126
6-Minute Walk Test (mean, SD)	509.86 (56.09)	525.93 (47.19)	532.60 (44.80)	<.0001
Waist circumference (mean, SD)	91.72 (14.55)	88.25 (13.89)	87.02 (13.97)	<.0001
Fasting blood glucose (mean, SD)	5.34 (1.09)	5.38 (1.18)	5.35 (0.88)	0.6899
Triglycerides (mean, SD)	1.89 (1.72)	1.68 (1.18)	1.64 (1.14)	0.1236
HDL cholesterol (mean, SD)	1.41 (0.49)	1.42 (0.39)	1.34 (0.41)	0.0042
Systolic blood pressure (mean, SD)	119.09 (13.58)	117.58 (13.44)	116.45 (12.90)	0.0294
Diastolic blood pressure (mean, SD)	75.47 (10.23)	74.23 (10.25)	74.47 (8.80)	0.1815
^a One-way ANOVA test				

(beta=-0.1221, $p<0.0001$) while over time their lung function improved and became significantly better compared to CC users. Factors negatively affecting FVC were age and history of lung disease, while being female and Caucasian ethnicity increased post-bronchodilator FVC.

Among the MetS components, waist circumference decreased over time in the observed participants. It was significantly higher for HTP users compared to CC users (beta=1.9311, $p<0.0001$). However, over time HTP users show significant decreases in waist circumference compared to CC users (beta (12-months)= -1.5208, $p<0.0001$; beta (24-months)= -1.2950, $p<0.01$).

DISCUSSION

To our knowledge, this is one of the few prospective studies which compares effect of shifting to HTP use in

a large population of long-term CC users who were unable to quit smoking. This study has shown that both HTP and CC use are associated with decline in lung function over time, HTP use was associated with a significantly lesser decline compared to CC users during the follow-up period. This study has also demonstrated that HTP users have experienced significant over time improvements in functional health outcomes compared to CC users. The results of the study suggest that shifting to HTP use might be less deleterious compared to continuation of CC use for experienced smokers (>10 pack years) who are not able to quit the habit.

This study demonstrates that lung function decreases significantly less for participants who shifted to HTP compared to CC users over time despite that it was significantly worse for HTP users at the baseline. While improvements in the health in this cohort can be

Table 3: Multivariable Repeated Measures Analyses Of Main Outcomes Over Time

	CAT score	FEV1	FVC	6-Minute Walk Test	Waist circumference	HDL cholesterol	Systolic blood pressure
Follow-up 12-months	-0.0526***	-0.0720***	-0.0808***	12.4523***	-1.9195***	0.0262	0.2261
Follow-up 24-months	-0.0612***	-0.0914***	-0.1937***	13.6561***	-2.3134***	-0.0543*	-0.2992
HTP use (ref. CC)	-0.0329***	-0.0124	-0.1221***	-2.8755	1.9311***	0.0543*	0.5329
Age	0.0007	-0.0423***	-0.0404***	-2.0043***	0.2589**	0.0055**	0.4054***
Female sex (ref. Male)	-0.0133*	1.0024***	1.2185***	27.5117***	10.9637***	-0.3055***	8.1992***
Pack years	0.0011***	-0.0034*	-0.0029	-0.4537**	0.1043*	-0.0024*	0.0780*
Caucasian ethnicity (ref. Asian)	0.0125**	0.1611***	0.2809***	5.5458*	0.6863	-0.0184	2.7464**
Previous history of lung disease (ref. No)	0.0785***	-0.2194**	-0.2248**	-3.0942	2.2175	0.0995	-0.7971
Not married (ref. Yes)	0.0051	0.0684*	0.0561	-2.0229	-0.3162	0.0399	-0.5410
12-months * HTP use (ref. CC)	0.0078	0.0254	0.1301***	5.6707*	-1.5208***	0.0016	-1.9072**
24-months * HTP use (ref. CC)	0.0194**	0.0602**	0.1802***	9.0380**	-1.2950**	-0.0274	-2.1922**
*Significant at <0.05 **Significant at <0.01 ***Significant at <0.0001							

attributed to a regular access to qualified physicians running this study, HTP users showed significantly better functional outcomes, including self-reported COPD scores, exercise tolerance, and MetS, components compared to CC users. These findings are supported by the existing literature with a systematic review of 15 studies demonstrating reduced health effects associated with HTP use when compared to CC use, especially considering the potential indirect effects of CC use on the chronic diseases [13].

A meta-analysis of ten nonblinded randomized clinical trials involving a total of 1766 participants demonstrated that the levels of 12 biomarkers of exposure were significantly lower for participants assigned to HTP compared to CC use. Moreover, out of 12 biomarkers of exposure eight were statistically equivalent and four significantly elevated when HTP use was compared to smoking abstinence [14]. In another randomized study participants who shifted to HTP use (n=488) demonstrated favorable changes after six months of follow-up compared to those continued smoking their preferred cigarette brand (n=496). There were statistically significant improvements in five out of eight biomarkers for smokers who switched to HTP when compared with those who continued to smoke CC [15].

In our previous study we compared 627 CC smokers and 308 IQOS users, men and women aged between 40 and 59 residing in Almaty, Kazakhstan matched by gender, age, education, and smoking history [9]. We compared spirometry measurements, the 6MWT, components of metabolic syndrome and anthropometric measurements as a part of the baseline and one-year assessments. We observed significantly better outcomes for HTP users in most of CAT scores, spirometry outcomes, and in some metabolic syndrome components. The changes in CAT score and in spirometry FEV1 over FVC ratios were worsening at higher pace for CC smokers compared to HTP users after one year of observation.

This study has several strengths, including large sample size (n=1200), low attrition rate (16%), and measurement of the study outcomes by experienced staff. There are several limitations to this study. The major limitation is that two years follow-up is not sufficient to study the effect of shifting to HTP use on chronic conditions. The other major limitation is that the cohort participants were recruited and followed up in healthcare centers which led to significant improvements in health outcomes for both CC and HTP users. This limits generalizability of the results of this study as not everyone has access to quality healthcare.

Additionally, over time decline in FEV1 and FVC observed in CC users falls within normal clinical variability and should be interpreted with caution. There might be some potential residual confounding that might explain associations reported in this study. However, the models were adjusted for important factors and the chance of significant residual confounding is low.

CONCLUSION

The results of this study demonstrate that shifting to HTP has potentially less deleterious effects on functional health outcomes compared to continued CC use for long-term smokers who cannot quit smoking. Future research should concentrate on further follow-up of this cohort to identify effects of shifting to HTP on existing and emerging chronic conditions, as well as health related measures and outcomes. While this study has shown shifting to HTP use to be less deleterious compared to CC use, the results of study should be interpreted with caution, and quitting smoking is preferential to continuous use of CC or HTP.

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DISCLOSURE

The authors report no conflicts of interest in this work.

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