Respiratory Function, Physical Capacity, and Metabolic Syndrome Components in Combustible Cigarettes and Heated Tobacco Products Users: a Five-Year Follow-Up Cohort Study

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Abstract: ***Purpose:*** Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide and is the fourth leading cause of death in Kazakhstan. Cigarette smoking is a prevalent risk factor for COPD. While quitting smoking is the preferred way to reduce COPD risk, 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 in long-term smokers compared to continued combustible cigarettes (CC) use. ***Patients and methods:*** A cohort of 1200 participants (393 HTP and 807 CC) aged 40-59 years with a minimum of 10 pack-year smoking history were recruited and followed for five years. The functional outcomes compared between HTP, CC users and No-Smokers (NS, people who stopping smoking) 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 (MIXED) were used to compare functional outcomes between visits and to test associations between health outcomes and smoking type (HTP vs. CC vs. NS) over time. ***Results:*** Out of 1200 participants 830 (466 CC users, 248 HTP users and 116 No-Smokers) remained in the study by the fifth year of follow up. Linear mixed models showed HTP use was associated with better CAT scores and HDL cholesterol level compared to CC users. Lung function (FVC) decrease was significantly less in HTP users. FEV, 6MWD, waist circumference, fasting blood glucose, triglycerides and diastolic blood pressure significantly changes over time, but without between-group difference in dynamic. ***Conclusion:*** This study demonstrated that HTP users experienced it to a significantly lesser decrease in lung function by FVC compared to CC users over time (in time dependent model), while demonstrating better stable levels in other functional outcomes. 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: Heated Tobacco Products, Combustible Cigarettes, Cohort Study, Health Outcomes, Smoking, COPD Self-Reported Score.

INTRODUCTION

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

Cigarette smoking is the most common risk factor for COPD [5]. The results of a previous 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 reduced functional exercise capacity such as ability to walk 450 meters within 6 minutes 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 reduce 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-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 within the group mean at baseline and 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 at four 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 five-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.

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MATERIAL 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 predominantly use HTP during the day (≥ 70% of time). We recruited 1200 participants (393 HTP and 807 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 60 months with functional outcomes and smoking status (HTP/CC/Quit smoking) measured at baseline, 12-, 24-, 36-, 48- and 60-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. KAPM was 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 (HTP/CC/Quit smoking), level of smoking exposure (in pack-years), passive smoking, history of lung disease, etc. The questionnaire contains covariates: 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 ≥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. Despite the fact that CAT was designed for patients with COPD, it 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.

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 at baseline using the Student's t-test for continuous variables and Chi-Square test for categorical variables. Type III test of fixed effects for multivariable linear mixed models was used to compare outcome measures at baseline, 12-. 24-, 36-, 48- and 60- months for HTP and CC users. Linear mixed models including repeated measures were performed to compare the effects of smoking status on: (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. The analysis was performed with models included time (at baseline, 12-, 24-, 36, 48- and 48- months) and with time as continuous variable. Also 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 was included in statistical models. All statistical analyses were done with IBM SPSS v28 and Metida.jl (Julia v1.8 package). A two-tailed p value of less than 0.05 was considered of statistical significance.

RESULTS

Recruited participants (N=1200) were followed-up for 60-months during which 30.67% of participants were lost to follow-up. 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. Smoking behavior by visits presented in Figure 1 and reflected in the contingency Table 2. There were no significant differences between CC and HTP users at baseline, except for CAT score, which was significantly lower for HTP group.

The dynamic of the main outcomes between baseline, 12-, 24-, 36-, 48- and 60- months follow-up are presented in Figures 2-11. 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 estimated marginal means of main outcomes' values at baseline, 12-, 24-, 36-, 48- and 60- months follow-up are presented in Tables 3-7 separately for CC users, HTP users and No-Smokers. Estimated marginal means of difference between smoking type groups presented at Table 9. The analyses show that all variables significantly changes over time (Table 8). In particular, CAT scores significantly decreased for both CC and HTP users, from 13.08 (SE 0.126) to 10.33 (SE 0.239) for CC users and from 12.87 (SE 0.148) to 9.97 (SD 0.167) for HTP users. The 6MWT increased from 517.0 (SE 3.50) to 540.9 (SE 3.91) for CC users and from 513.9 (SE 4.16) to 538.3 (SE 4.77) for HTP users (both P<.0001).

For the models with time was used as continuous variable statistically significant difference between dynamic in HTP and CC groups was found for CAT score and FVC (Table 9).

The coefficients of repeated measures analyses of main outcomes with smoking status (HTP vs CC) as main predictor are presented in Table 10. Smoking type was significantly associated CAT scores and HDL cholesterol levels.

The CAT scores have improved over time for both CC and HTP users (p<0.0001), though HTP smoking was significantly associated with lower CAT scores for 60-month follow-up compared to CC smokers (p<0.0001). Having larger number of pack years, female sex 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 dynamics for HTP users was significantly better compared to CC users (p<0.0001). Factors negatively affecting FVC were age and history of lung disease and being female.

Among the MetS components, waist circumference and triglycerides decreased over time in the observed participants while fasting blood glucose and diastolic blood pressure increased.

Figure 1: Smoking behavior by visits.

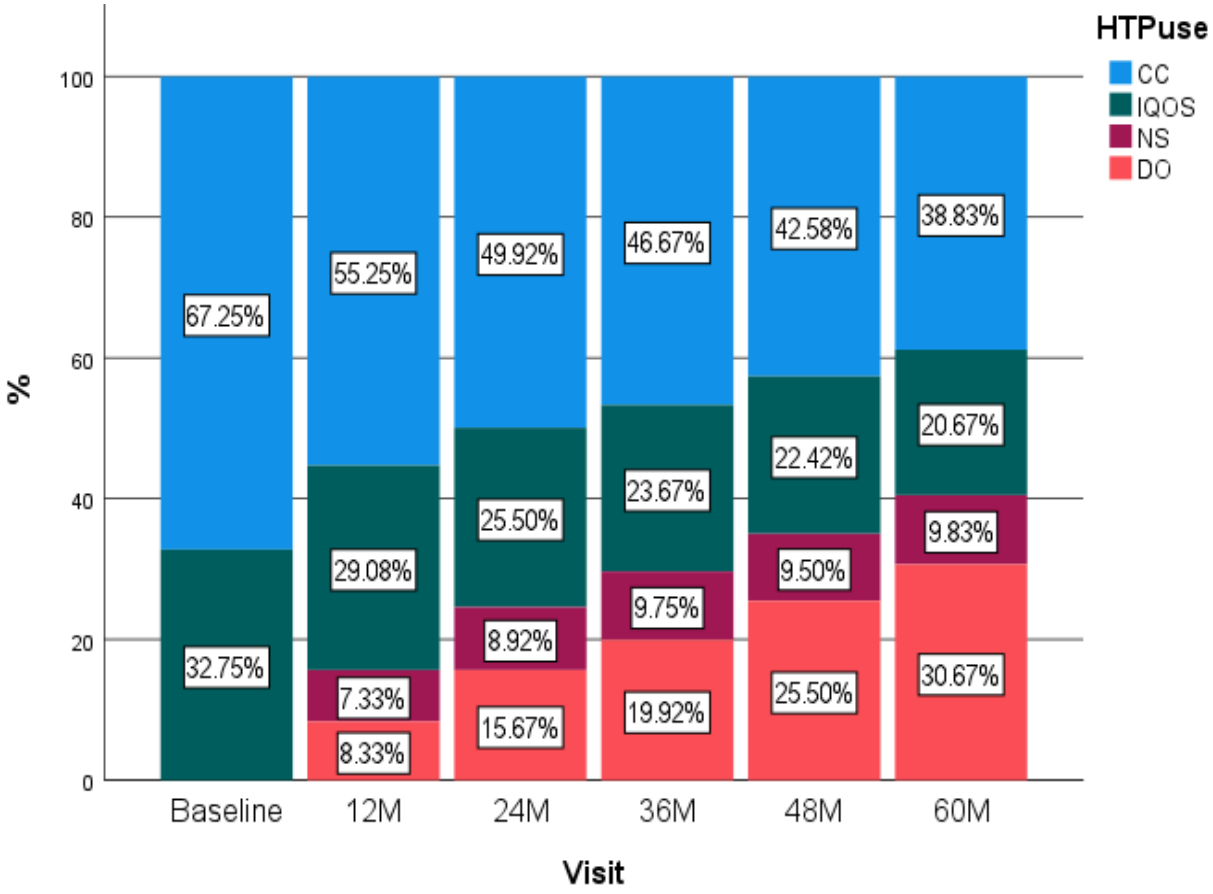

Figure 2: Estimated marginal means of CAT score.

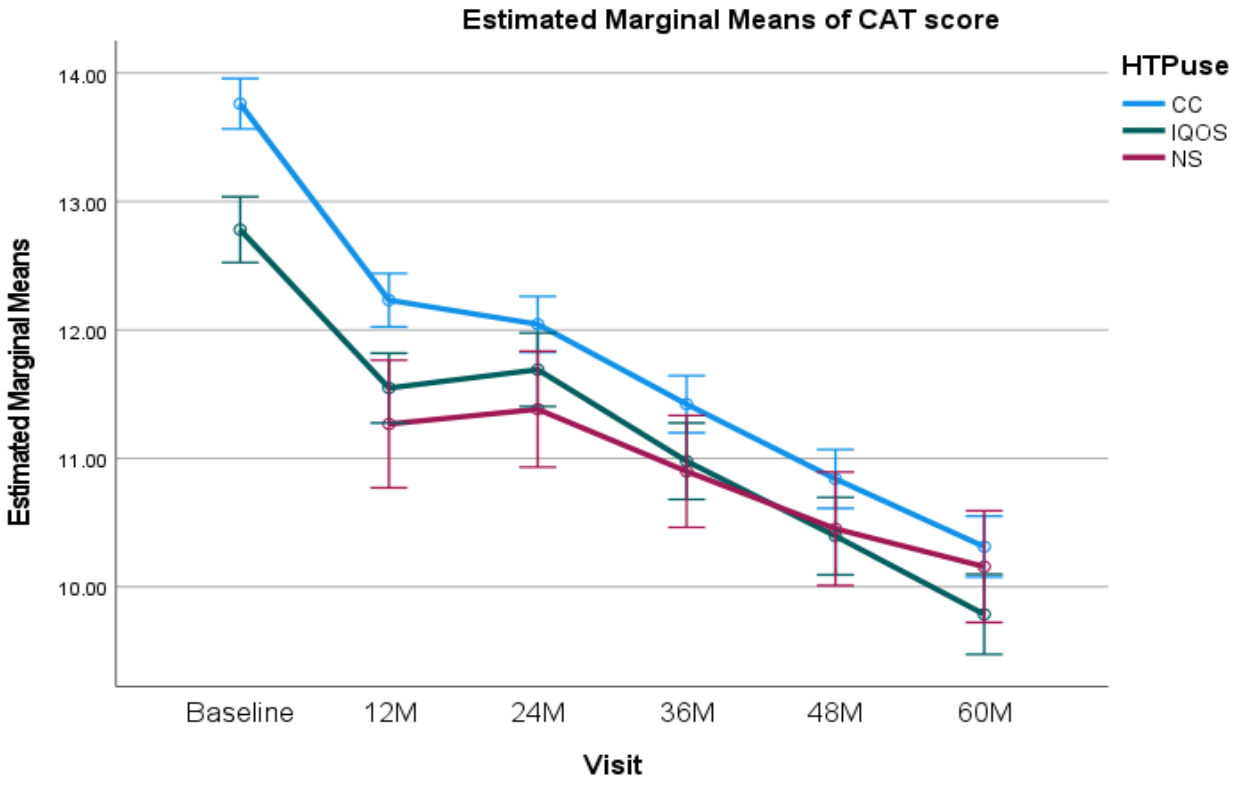

Figure 3: Estimated marginal means of FEV.

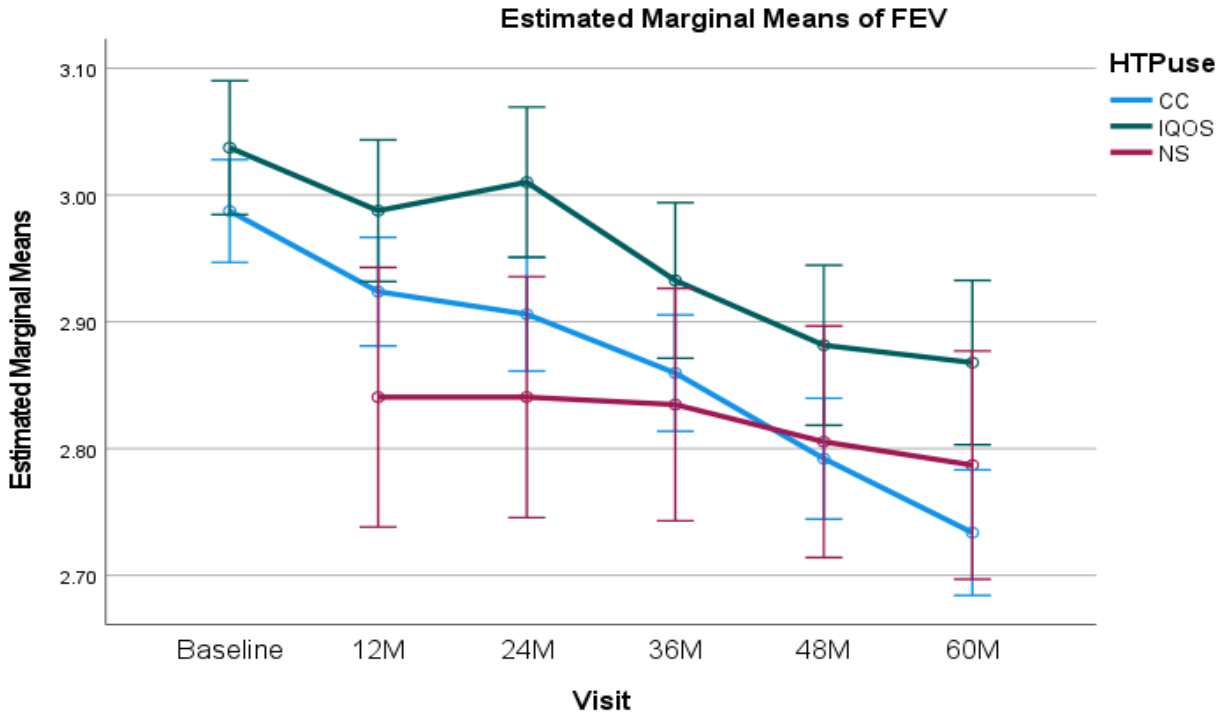

Figure 4: Estimated marginal means of FVC.

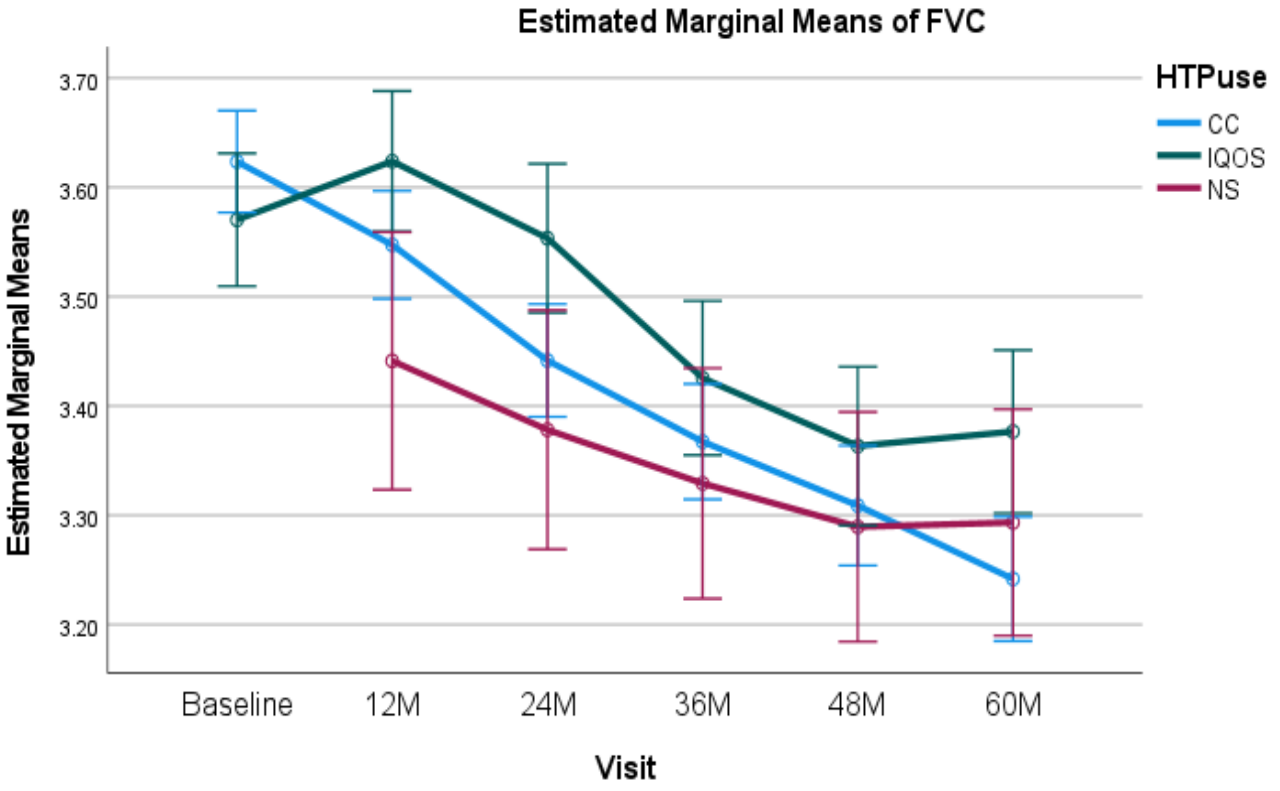

Figure 5: Estimated marginal means of 6MWT.

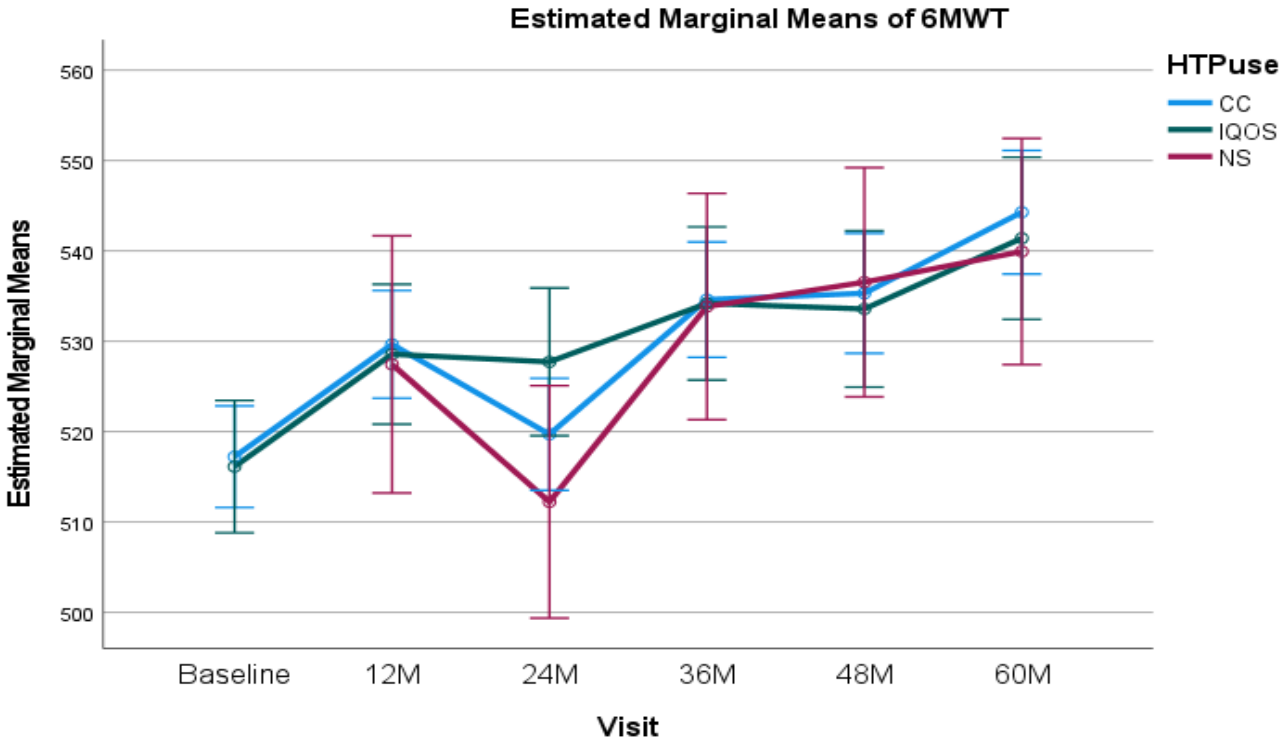

Figure 6: Estimated marginal means of Waist.

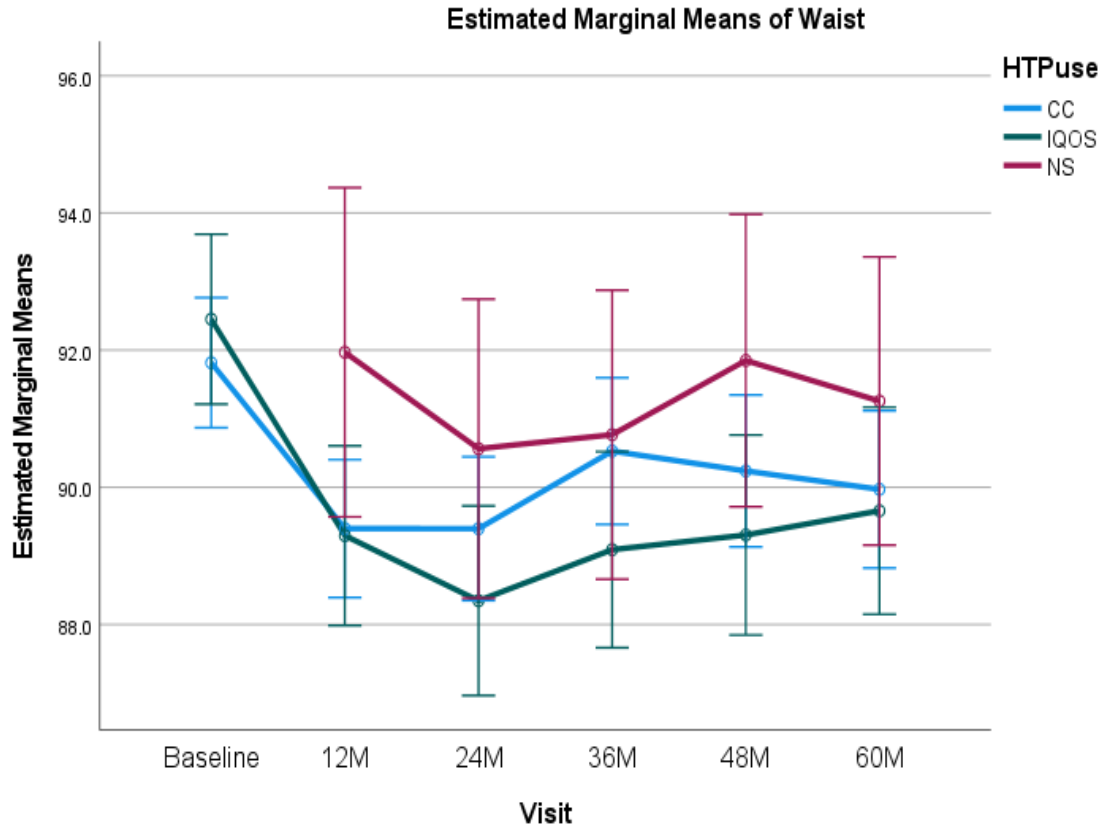

Figure 7: Estimated marginal means of Glucose.

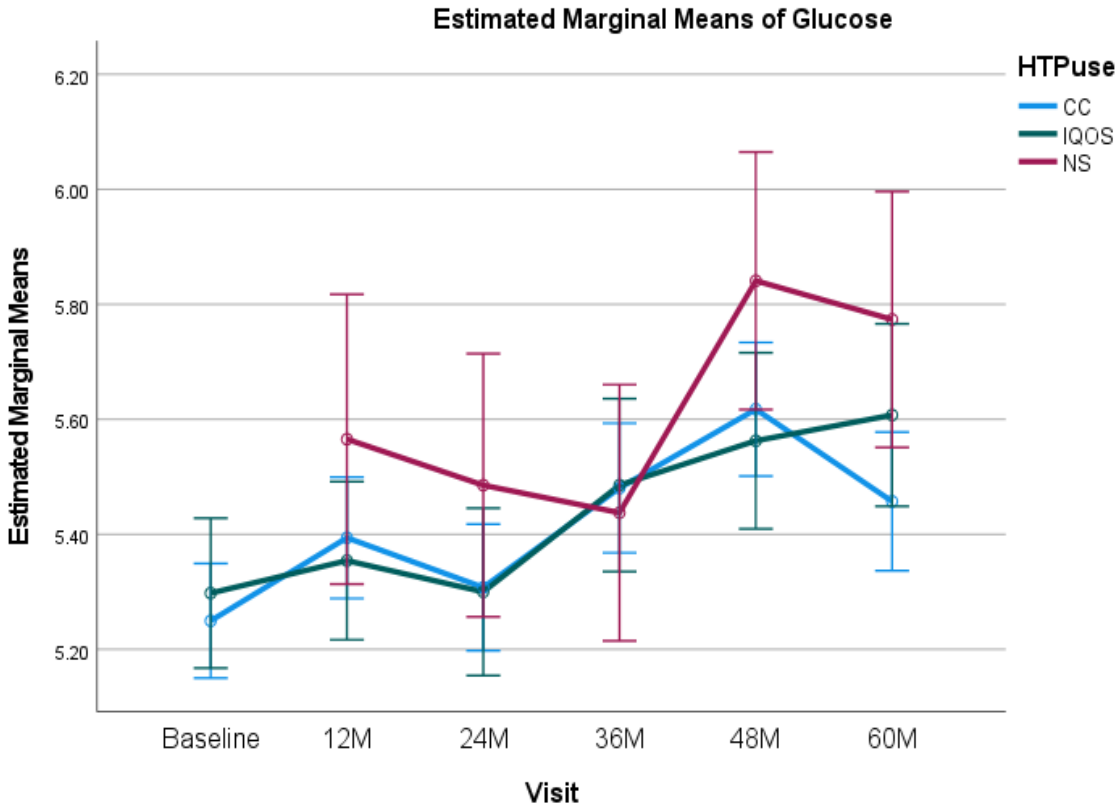

Figure 8: Estimated marginal means of Tryglycerides.

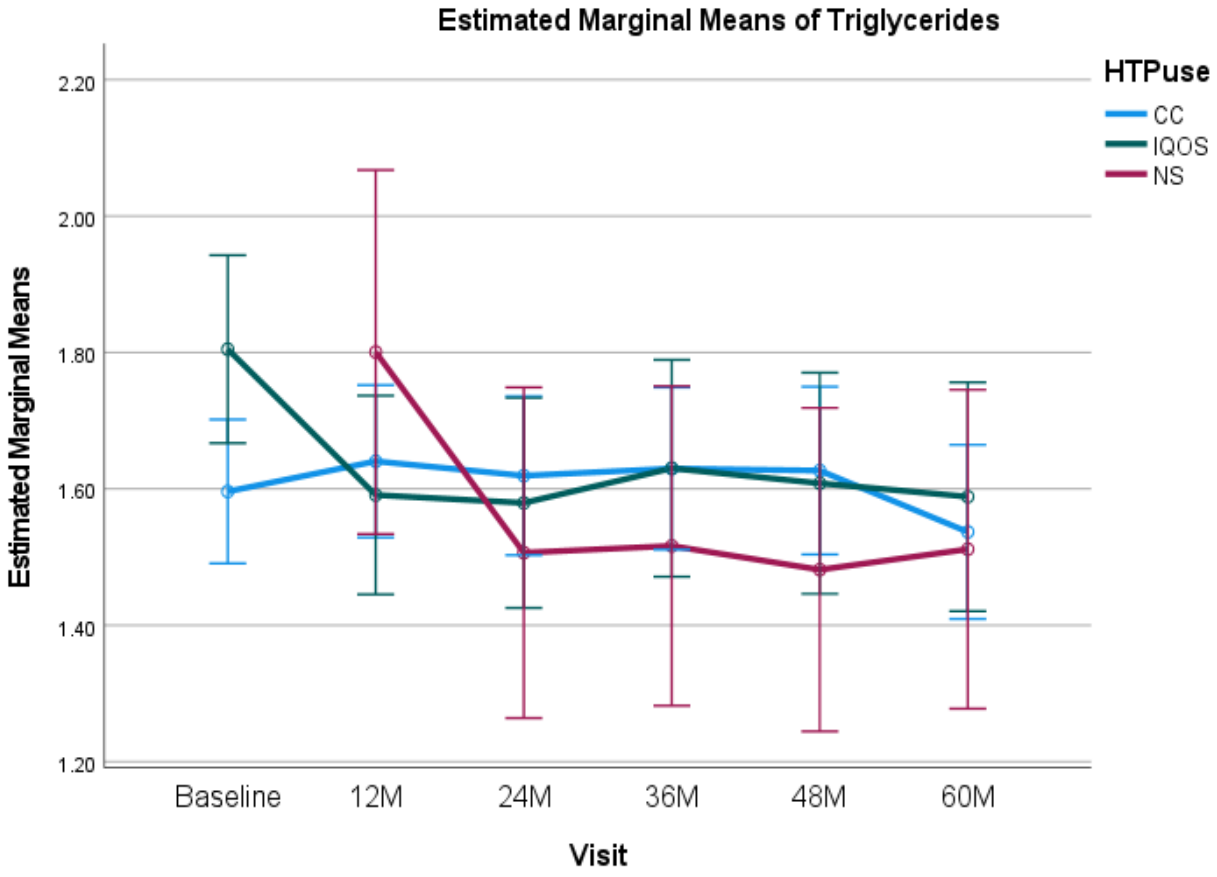

Figure 9: Estimated marginal means of HDL cholesterol.

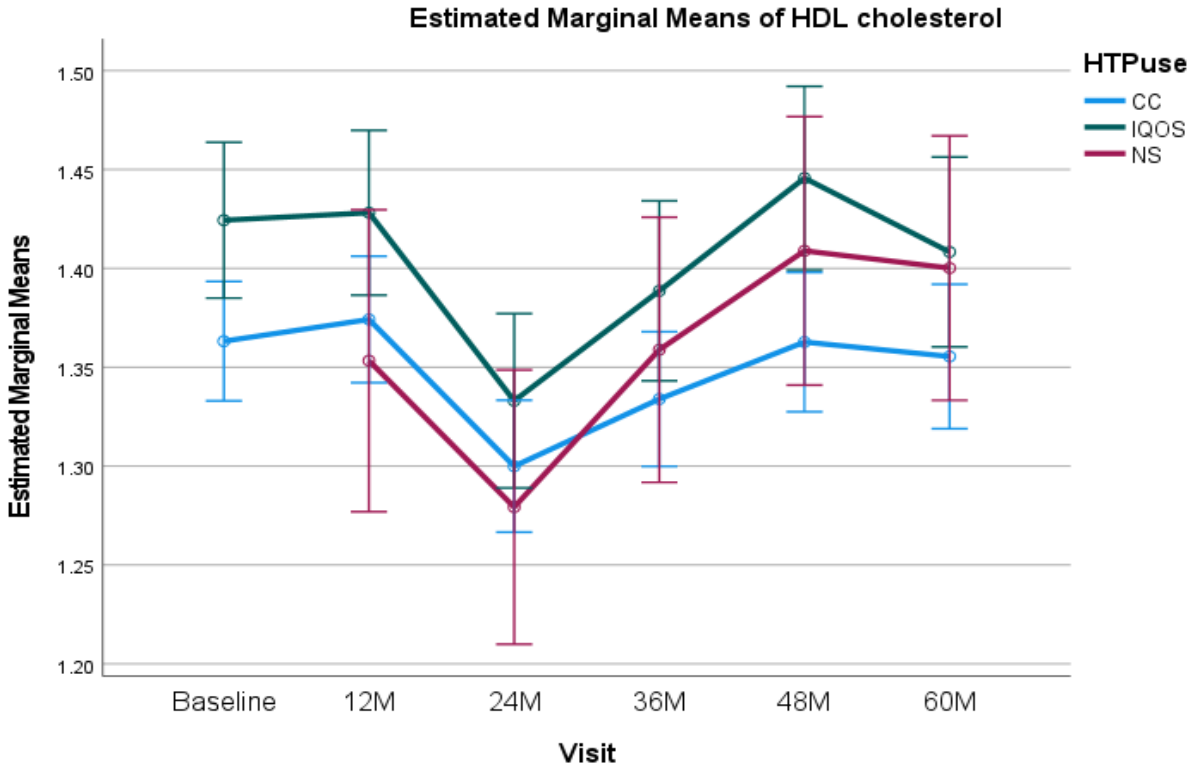

Figure 10: Estimated marginal means of SBP.

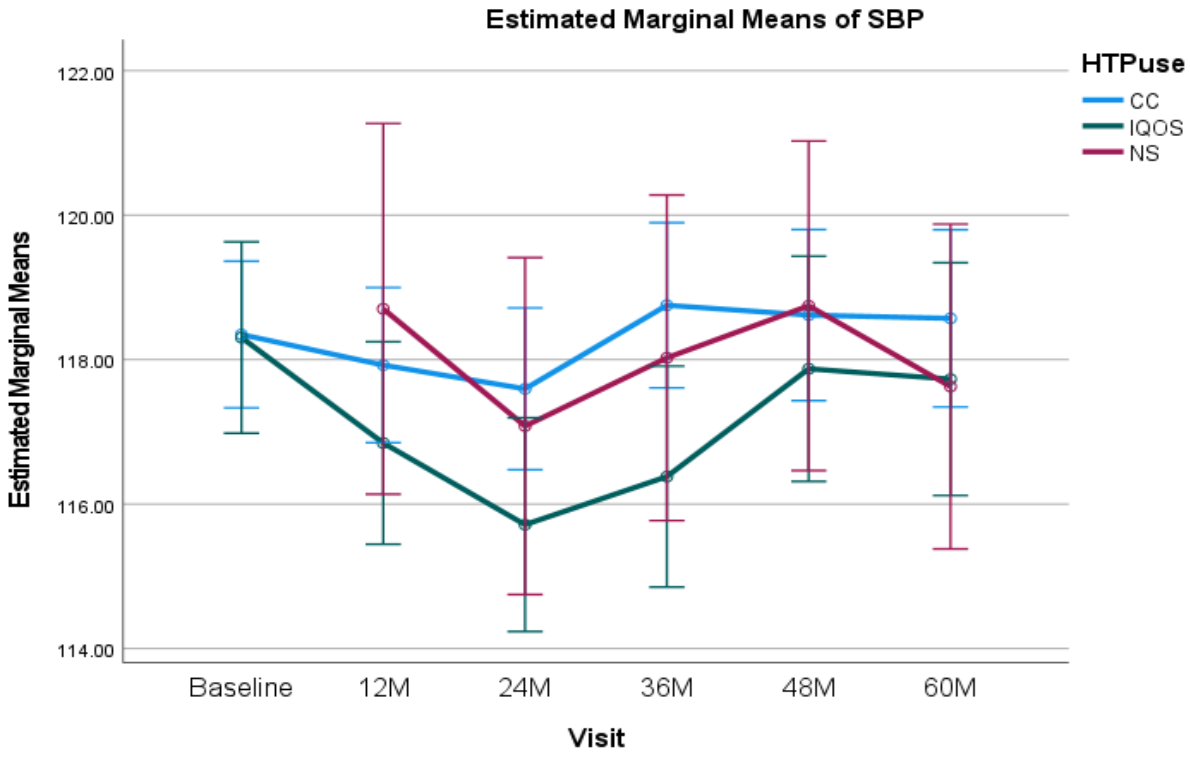

Figure 11: Estimated marginal means of DBP.

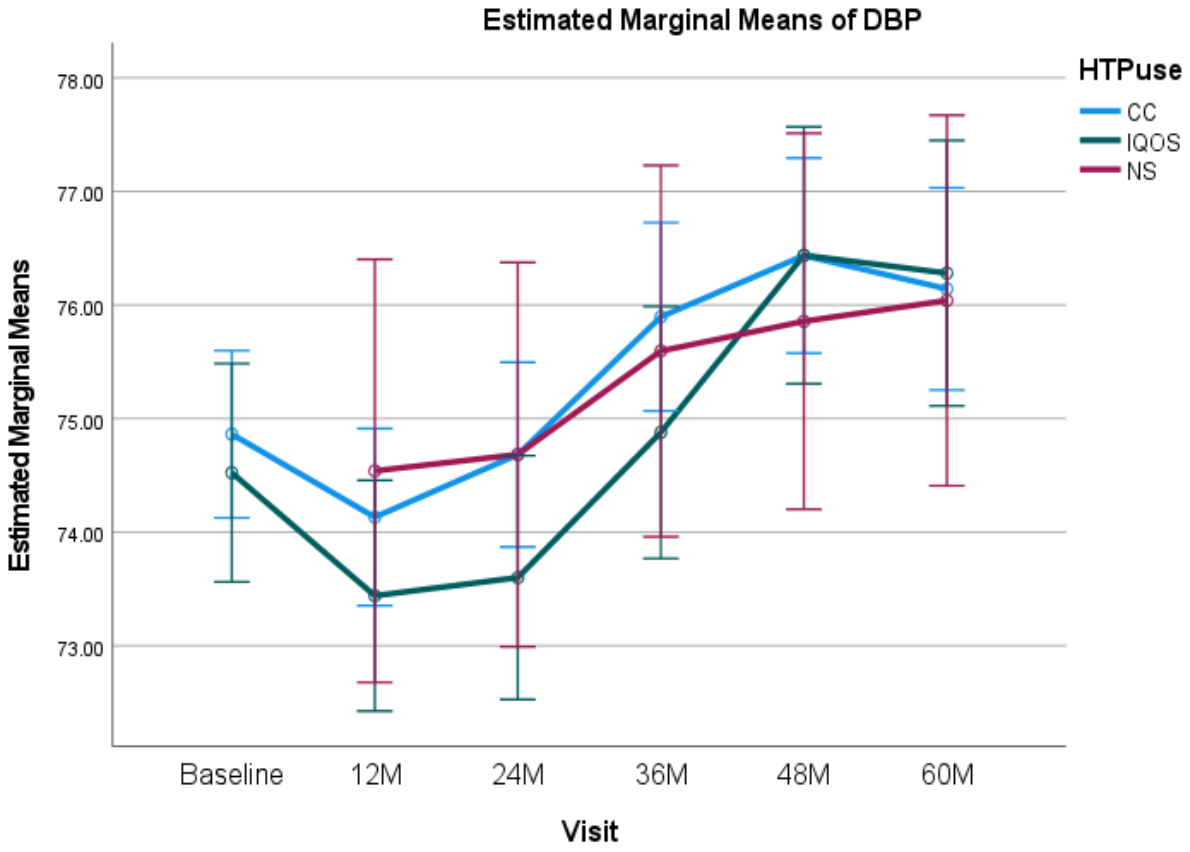

Table 1: Baseline demographics of the subjects on the study compared using descriptive statistics.

	CC (n=807)	HTP (n=393)	p-value
Age (mean, SD)	49.20 (5.21)	48.85 (5.13)	0.279[a]
Ethnicity (n, %)			
Asian	573 (71.0%)	275 (29.0%)	0.997[b]
Caucasian	234 (71.00%)	114 (29.0%)	
Sex (n, %)			
Male	397 (49.2%)	197 (50.1%)	0.762[b]
Female	410 (50.8%)	196 (49.9%)	
Married (n, %)			
No	226 (28.0%)	93 (23.7%)	0.110[b]
Yes	581 (72.0%)	300 (76.3%)	
History of lung disease (n, %)			
No	757 (93.8%)	370 (94.1%)	0.815[b]
Yes	50 (6.2%)	23 (5.9%)	
Pack years (mean, SD)	22.87 (10.53)	22.66 (10.59)	0.754[a]
CAT score (mean, SD)	12.84 (3.17)	11.85 (2.89)	<.001[a]
FEV (mean, SD)	3.11 (0.74)	3.17 (0.71)	0.215[a]
FVC (mean, SD)	3.74 (0.88)	3.69 (0.83)	0.349[a]
6-Minute Walk Test (mean, SD)	520.69 (52.47)	520.19 (55.66)	0.879[a]

a-Student's t test (2-sided) b-Chi Square test (2-sided)

Table 2: Crosstabulation: Visit by HTPuse.

			HTPuse				Total
			CC	IQOS	NS	DO	
Visit	Baseline	Count	807	393	0	0	1200
		% within Visit	67.3%	32.8%	0.0%	0.0%	100.0%
		% within HTPuse	22.4%	21.3%	0.0%	0.0%	16.7%
	Follow-up 12-months	Count	663	349	88	100	1200
		% within Visit	55.3%	29.1%	7.3%	8.3%	100.0%
		% within HTPuse	18.4%	18.9%	16.2%	8.3%	16.7%
	Follow-up 24-months	Count	599	306	107	188	1200
		% within Visit	49.9%	25.5%	8.9%	15.7%	100.0%
		% within HTPuse	16.6%	16.5%	19.7%	15.7%	16.7%
	Follow-up 36-months	Count	560	284	117	239	1200
		% within Visit	46.7%	23.7%	9.8%	19.9%	100.0%
		% within HTPuse	15.5%	15.4%	21.5%	19.9%	16.7%
	Follow-up 48-months	Count	511	269	114	306	1200
		% within Visit	42.6%	22.4%	9.5%	25.5%	100.0%
		% within HTPuse	14.2%	14.5%	21.0%	25.5%	16.7%
	Follow-up 60-months	Count	466	248	118	368	1200
		% within Visit	38.8%	20.7%	9.8%	30.7%	100.0%
		% within HTPuse	12.9%	13.4%	21.7%	30.6%	16.7%

DO – Drop Out

Table 3: Estimated marginal means CC, HTP users and no-smokers by time (visits) for CAT_score.

			Visit					
			Baseline	12-month follow-up	24-month follow-up	36-month follow-up	48-month follow-up	60-month follow-up
CAT score[1]								
CC	**Mean**		13.808[2]	12.243[2]	12.039[2]	11.435[2]	10.849[2]	10.332[2]
	Std. Error		0.126	0.129	0.132	0.134	0.136	0.139
	95% Confidence Interval	**Lower Bound**	13.562	11.990	11.780	11.173	10.582	10.060
		Upper Bound	14.055	12.497	12.298	11.698	11.115	10.604
HTP	**Mean**		12.872[2]	11.634[2]	11.775[2]	11.101[2]	10.567[2]	9.970[2]
	Std. Error		0.148	0.153	0.159	0.163	0.164	0.167
	95% Confidence Interval	**Lower Bound**	12.582	11.333	11.464	10.782	10.247	9.642
		Upper Bound	13.161	11.935	12.086	11.420	10.888	10.298
NS	**Mean**		.[2,3]	11.531[2]	11.539[2]	11.010[2]	10.517[2]	10.364[2]
	Std. Error		.	0.236	0.218	0.212	0.214	0.211
	95% Confidence Interval	**Lower Bound**	.	11.068	11.111	10.595	10.098	9.951
		Upper Bound	.	11.994	11.966	11.425	10.936	10.776

1. Dependent Variable.
2. Covariates appearing in the model are evaluated at the following values: Age ≈ 49.18, Pack years ≈ 22.64.
3. This level combination of factors is not observed, thus the corresponding population marginal mean is not estimable.

Table 4: Estimated marginal means CC, HTP users and no-smokers by time (visits) for FEV and FVC.

			Visit					
			Baseline	12-month follow-up	24-month follow-up	36-month follow-up	48-month follow-up	60-month follow-up
FEV[1]								
CC	**Mean**		2.991[2]	2.920[2]	2.904[2]	2.850[2]	2.785[2]	2.739[2]
	Std. Error		0.030	0.030	0.030	0.030	0.031	0.031
	95% Confidence Interval	**Lower Bound**	2.932	2.861	2.844	2.791	2.725	2.679
		Upper Bound	3.050	2.980	2.963	2.910	2.845	2.799
HTP	**Mean**		2.967[2]	2.916[2]	2.925[2]	2.873[2]	2.820[2]	2.789[2]
	Std. Error		0.032	0.032	0.032	0.032	0.033	0.033
	95% Confidence Interval	**Lower Bound**	2.905	2.854	2.862	2.810	2.756	2.725
		Upper Bound	3.029	2.979	2.988	2.937	2.884	2.854
NS	**Mean**		.[2,3]	2.864[2]	2.871[2]	2.812[2]	2.786[2]	2.767[2]
	Std. Error		.	0.038	0.036	0.036	0.036	0.035
	95% Confidence Interval	**Lower Bound**	.	2.791	2.799	2.741	2.716	2.698
		Upper Bound	.	2.938	2.942	2.882	2.857	2.837

FVC[1]								
CC	**Mean**		3.632[2]	3.553[2]	3.444[2]	3.361[2]	3.297[2]	3.242[2]
	Std. Error		0.034	0.034	0.035	0.035	0.035	0.035
	95% Confidence Interval	**Lower Bound**	3.565	3.486	3.376	3.293	3.228	3.173
		Upper Bound	3.699	3.621	3.512	3.429	3.366	3.311
HTP	**Mean**		3.505[2]	3.550[2]	3.476[2]	3.371[2]	3.308[2]	3.292[2]
	Std. Error		0.036	0.037	0.037	0.038	0.038	0.038
	95% Confidence Interval	**Lower Bound**	3.434	3.478	3.403	3.297	3.234	3.217
		Upper Bound	3.576	3.622	3.549	3.444	3.383	3.366
NS	**Mean**		.[2,3]	3.469[2]	3.394[2]	3.290[2]	3.258[2]	3.270[2]
	Std. Error		.	0.045	0.043	0.043	0.042	0.042
	95% Confidence Interval	**Lower Bound**	.	3.381	3.309	3.206	3.175	3.187
		Upper Bound	.	3.557	3.479	3.373	3.341	3.352

1. Dependent Variable.
2. Covariates appearing in the model are evaluated at the following values: Age ≈ 49.18, Pack years ≈ 22.64.
3. This level combination of factors is not observed, thus the corresponding population marginal mean is not estimable.

Table 5: Estimated marginal means CC, HTP users and no-smokers by time (visits) for 6-Minute Walk Test and Waist circumference.

			Visit					
			Baseline	**12-month follow-up**	**24-month follow-up**	**36-month follow-up**	**48-month follow-up**	**60-month follow-up**
6-Minute Walk Test[1]								
CC	**Mean**		517.015[2]	528.937[2]	518.519[2]	532.555[2]	531.264[2]	540.941[2]
	Std. Error		3.501	3.611	3.697	3.761	3.845	3.912
	95% Confidence Interval	**Lower Bound**	510.150	521.856	511.269	525.180	523.724	533.270
		Upper Bound	523.880	536.019	525.770	539.931	538.804	548.612
HTP	**Mean**		513.948[2]	527.473[2]	525.558[2]	531.786[2]	530.444[2]	538.344[2]
	Std. Error		4.160	4.327	4.488	4.596	4.652	4.772
	95% Confidence Interval	**Lower Bound**	505.792	518.988	516.758	522.776	521.323	528.988
		Upper Bound	522.104	535.958	534.358	540.797	539.565	547.700
NS	**Mean**		.[2,3]	520.904[2]	510.971[2]	531.547[2]	536.786[2]	539.369[2]
	Std. Error		.	6.840	6.278	6.128	6.194	6.103
	95% Confidence Interval	**Lower Bound**	.	507.495	498.663	519.534	524.644	527.405
		Upper Bound	.	534.313	523.279	543.560	548.927	551.333
Waist circumference[1]								
CC	**Mean**		91.979[2]	90.104[2]	89.816[2]	90.762[2]	90.839[2]	90.910[2]
	Std. Error		0.708	0.712	0.714	0.716	0.718	0.720
	95% Confidence Interval	**Lower Bound**	90.590	88.708	88.415	89.358	89.431	89.497
		Upper Bound	93.368	91.500	91.218	92.166	92.247	92.322
HTP	**Mean**		93.144[2]	89.871[2]	89.754[2]	90.851[2]	91.234[2]	91.066[2]
	Std. Error		0.735	0.740	0.746	0.749	0.750	0.755

	95% Confidence Interval	Lower Bound	91.703	88.419	88.292	89.382	89.763	89.586
		Upper Bound	94.586	91.324	91.217	92.321	92.706	92.546
NS	Mean		.[2,3]	91.458[2]	91.114[2]	91.964[2]	91.944[2]	92.356[2]
	Std. Error		.	0.837	0.813	0.804	0.806	0.801
	95% Confidence Interval	Lower Bound	.	89.816	89.521	90.388	90.363	90.784
		Upper Bound	.	93.101	92.708	93.540	93.525	93.927

1. Dependent Variable.
2. Covariates appearing in the model are evaluated at the following values: Age ≈ 49.18, Pack years ≈ 22.64.
3. This level combination of factors is not observed, thus the corresponding population marginal mean is not estimable.

Table 6: Estimated marginal means CC, HTP users and no-smokers by time (visits) for fasting blood glucose, triglycerides and HDL cholesterol.

			Visit					
			Baseline	12-month follow-up	24-month follow-up	36-month follow-up	48-month follow-up	60-month follow-up
Fasting blood glucose[1]								
CC	Mean		5.302[2]	5.459[2]	5.375[2]	5.580[2]	5.695[2]	5.578[2]
	Std. Error		0.071	0.072	0.073	0.073	0.074	0.075
	df		1459.203	1535.129	1601.555	1638.018	1689.208	1750.595
	95% Confidence Interval	Lower Bound	5.163	5.318	5.232	5.436	5.550	5.431
		Upper Bound	5.441	5.601	5.518	5.724	5.839	5.724
HTP	Mean		5.359[2]	5.481[2]	5.458[2]	5.619[2]	5.717[2]	5.737[2]
	Std. Error		0.078	0.080	0.081	0.082	0.083	0.084
	df		1957.888	2106.090	2256.085	2349.304	2397.647	2508.624
	95% Confidence Interval	Lower Bound	5.206	5.324	5.298	5.458	5.554	5.572
		Upper Bound	5.512	5.637	5.617	5.781	5.879	5.902
NS	Mean		.[2,3]	5.396[2]	5.466[2]	5.507[2]	5.785[2]	5.759[2]
	Std. Error		.	0.106	0.100	0.098	0.098	0.098
	df		.	4547.563	4080.663	3939.052	3964.077	3917.850
	95% Confidence Interval	Lower Bound	.	5.188	5.269	5.314	5.592	5.567
		Upper Bound	.	5.604	5.662	5.699	5.978	5.951
Triglycerides[1]								
CC	Mean		1.632[2]	1.671[2]	1.626[2]	1.640[2]	1.607[2]	1.521[2]
	Std. Error		0.072	0.074	0.075	0.075	0.076	0.077
	95% Confidence Interval	Lower Bound	1.490	1.527	1.479	1.493	1.458	1.370
		Upper Bound	1.774	1.815	1.772	1.787	1.756	1.671
HTP	Mean		1.814[2]	1.617[2]	1.640[2]	1.682[2]	1.700[2]	1.638[2]
	Std. Error		0.081	0.083	0.085	0.086	0.087	0.088
	95% Confidence Interval	Lower Bound	1.656	1.455	1.474	1.513	1.530	1.466
		Upper Bound	1.973	1.780	1.807	1.850	1.870	1.810
NS	Mean		.[2,3]	1.829[2]	1.558[2]	1.632[2]	1.589[2]	1.602[2]
	Std. Error		.	0.114	0.107	0.104	0.105	0.104

	95% Confidence Interval	**Lower Bound**	.	1.605	1.348	1.427	1.383	1.398
		Upper Bound	.	2.053	1.768	1.837	1.796	1.805
HDL cholesterol[1]								
CC	**Mean**		1.363[2]	1.368[2]	1.297[2]	1.336[2]	1.362[2]	1.359[2]
	Std. Error		0.021	0.022	0.022	0.022	0.022	0.022
	95% Confidence Interval	**Lower Bound**	1.321	1.325	1.255	1.293	1.319	1.316
		Upper Bound	1.404	1.410	1.340	1.379	1.406	1.403
HTP	**Mean**		1.422[2]	1.435[2]	1.318[2]	1.362[2]	1.421[2]	1.388[2]
	Std. Error		0.023	0.024	0.024	0.024	0.024	0.025
	95% Confidence Interval	**Lower Bound**	1.376	1.388	1.271	1.314	1.373	1.340
		Upper Bound	1.467	1.481	1.365	1.410	1.469	1.437
NS	**Mean**		.[2,3]	1.364[2]	1.297[2]	1.342[2]	1.392[2]	1.358[2]
	Std. Error		.	0.031	0.029	0.028	0.029	0.028
	95% Confidence Interval	**Lower Bound**	.	1.304	1.240	1.287	1.336	1.303
		Upper Bound	.	1.425	1.354	1.398	1.448	1.414

1. Dependent Variable.
2. Covariates appearing in the model are evaluated at the following values: Age ≈ 49.18, Pack years ≈ 22.64.
3. This level combination of factors is not observed, thus the corresponding population marginal mean is not estimable.

Table 7: Estimated marginal means CC, HTP users and no-smokers by time (visits) for systolic and diastolic blood pressure.

			Visit					
			Baseline	**12-month follow-up**	**24-month follow-up**	**36-month follow-up**	**48-month follow-up**	**60-month follow-up**
Systolic blood pressure[1]								
CC	**Mean**		118.556[2]	118.679[2]	118.240[2]	119.268[2]	119.111[2]	119.612[2]
	Std. Error		0.711	0.721	0.730	0.734	0.741	0.749
	df		1523.350	1605.544	1678.078	1713.331	1774.294	1841.182
	95% Confidence Interval	**Lower Bound**	117.162	117.264	116.808	117.828	117.657	118.143
		Upper Bound	119.950	120.093	119.672	120.708	120.565	121.081
HTP	**Mean**		119.450[2]	117.669[2]	116.829[2]	117.967[2]	119.565[2]	118.767[2]
	Std. Error		0.786	0.804	0.820	0.831	0.835	0.847
	df		2052.664	2215.649	2372.700	2472.546	2529.237	2636.771
	95% Confidence Interval	**Lower Bound**	117.909	116.093	115.220	116.338	117.927	117.106
		Upper Bound	120.991	119.245	118.438	119.596	121.202	120.427
NS	**Mean**		.[2,3]	118.761[2]	117.847[2]	119.363[2]	119.743[2]	118.975[2]
	Std. Error		.	1.080	1.015	0.992	0.999	0.987
	df		.	4746.502	4285.048	4107.630	4170.315	4086.195
	95% Confidence Interval	**Lower Bound**	.	116.645	115.856	117.418	117.785	117.040
		Upper Bound	.	120.878	119.838	121.307	121.701	120.909

Diastolic blood pressure[1]								
CC	Mean		74.913[2]	74.493[2]	74.989[2]	76.094[2]	76.714[2]	76.734[2]
	Std. Error		0.507	0.516	0.523	0.527	0.533	0.539
	df		1595.253	1695.231	1784.088	1827.516	1903.453	1987.114
	95% Confidence Interval	Lower Bound	73.919	73.481	73.963	75.061	75.669	75.676
		Upper Bound	75.907	75.504	76.016	77.128	77.760	77.792
HTP	Mean		75.171[2]	73.951[2]	74.220[2]	75.684[2]	77.096[2]	76.502[2]
	Std. Error		0.569	0.584	0.598	0.607	0.611	0.621
	df		2205.885	2398.105	2585.340	2704.859	2777.172	2903.111
	95% Confidence Interval	Lower Bound	74.055	72.805	73.047	74.494	75.899	75.285
		Upper Bound	76.287	75.096	75.393	76.874	78.294	77.719
NS	Mean		.[2,3]	74.496[2]	74.975[2]	76.468[2]	76.416[2]	76.815[2]
	Std. Error		.	0.814	0.761	0.742	0.748	0.738
	df		.	5128.457	4706.291	4540.765	4603.744	4528.974
	95% Confidence Interval	Lower Bound	.	72.901	73.483	75.014	74.950	75.368
		Upper Bound	.	76.090	76.467	77.923	77.882	78.262

1. Dependent Variable.
2. Covariates appearing in the model are evaluated at the following values: Age ≈ 49.18, Pack years ≈ 22.64.
3. This level combination of factors is not observed, thus the corresponding population marginal mean is not estimable.

Table 8: Significance for Type III Tests of Fixed Effects.

Source	CAT score	FEV	FVC	6-Minute Walk Test	Waist circumference	Fasting blood glucose	Triglycerides	HDL cholesterol	Systolic blood pressure	Diastolic blood pressure
Intercept	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Visit	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.005	<0.001	<0.001	<0.001
HTP use	<0.001	0.037	0.007	0.698	<0.001	0.225	0.273	<0.001	0.344	0.712
Age	0.077	<0.001	<0.001	<0.001	<0.001	<0.001	0.363	0.022	<0.001	0.002
Sex	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Pack years	<0.001	0.106	0.560	<0.001	0.005	0.141	0.995	0.079	0.002	0.002
Ethnicity	0.117	0.581	0.711	0.241	0.902	0.481	0.853	0.885	0.494	0.475
Previous history of lung disease	<0.001	<0.001	<0.001	0.130	0.075	0.700	0.241	0.251	0.309	0.049
Marital status	0.493	0.466	0.434	0.829	0.197	0.639	0.195	0.033	0.258	0.490
Visit * HTP use	<0.001	0.005	<0.001	0.373	0.025	0.244	0.039	0.213	0.018	0.538

Table 9: Multivariable repeated measures analyses of main outcomes over time.

	CAT score	FEV	FVC	6-Minute Walk Test	Waist circum-ference	Fasting blood glucose	Triglycerides	HDL cholesterol	Systolic blood pressure	Diastolic blood pressure
HTP vs CC difference EMM (SE)	-0.465*** (0.0853)	0.017 (0.012)	-0.0045 (0.0153)	-0.280 (2.42)	0.252 (0.242)	0.0636 (0.0389)	0.0659 (0.0423)	0.0433*** (0.0111)	-0.537 (0.397)	-0.219 (0.301)
NS vs CC difference EMM (SE)	-0.792*** (0.113)	-0.0448 (0.0136)	-0.0854 (0.0177)	-0.290 (3.28)	1.032 (0.271)	0.0844 (0.0468)	0.0260 (0.0517)	0.0031 (0.0132)	0.027 (0.479)	0.178 (0.372)
CC dynamic 1/year (SE)	-0.606*** (0.024)	-0.0492*** (0.00384)	-0.0782*** (0.0048)	4.42*** (0.57)	-0.219** (0.075)	0.0477*** (0.0122)	-0.0249* (0.0123)	-0.0018 (0.0035)	0.1323 (0.1133)	0.348*** (0.086)
HTP vs CC dynamic difference 1/year (SE)	0.080* (0.040)	0.0105 (0.0060)	0.0293*** (0.0076)	-0.057 (0.95)	-0.184 (0.115)	0.0222 (0.0194)	0.0012 (0.0201)	-0.0062 (0.0056)	-0.211682 0.182937	0.044 (0.141)
NS vs CC dynamic difference 1/year (SE)	0.272 (0.062)	0.0308** (0.0088)	0.0385** (0.0111)	-0.213 (1.59)	0.094 (0.161)	0.0384 (0.0301)	-0.0297 (0.0311)	0.0128 (0.0082)	-0.386773 0.285717	-0.155 (0.225)

*Significant at <.05
**Significant at <.01
***Significant at <.0001

Table 10: Multivariable repeated measures analyses of main outcomes (coefficients).

	CAT score	FEV	FVC	6-Minute Walk Test	Waist circumference	Fasting blood glucose	Triglycerides	HDL cholesterol	Systolic blood pressure	Diastolic blood pressure
(Intercept)	10.97***	5.80***	6.52***	649.5***	82.47***	4.27***	1.75***	0.985***	103.5***	69.55***
Follow-up 12-months	-1.565***	-0.0705***	-0.0786***	11.922***	-1.875***	0.157***	0.0391	0.0049	0.123	-0.420
Follow-up 24-months	-1.769***	-0.0870***	-0.188***	1.505	-2.163***	0.0729	-0.0065	-0.0654***	-0.316	0.0764
Follow-up 36-months	-2.373***	-0.141***	-0.271***	15.540***	-1.217***	0.278***	0.0077	-0.0264*	0.712	1.182*
Follow-up 48-months	-2.960***	-0.206***	-0.335***	14.249***	-1.140***	0.393***	-0.025	-0.0004	0.555	1.802***
Follow-up 60-months	-3.476***	-0.252***	-0.390***	23.926***	-1.069***	0.275***	-0.111	-0.0035	1.056*	1.821***
HTP use (ref. CC)	-0.936***	-0.0239	-0.127***	-3.067	1.165***	0.057	0.182**	0.059***	0.894	0.258
No-smokers (ref. CC)	-0.712**	-0.0334	-0.050	-8.033	1.354**	0.0906	0.158	-0.0034	0.083	0.0027
Age	0.0180	-0.0430**	-0.043***	-2.062***	0.247***	0.0229**	0.0056	0.0043*	0.348***	0.137**
Female sex (ref. Male)	0.370**	-0.948***	-1.145***	-24.742***	-11.195***	-0.376***	-0.538***	0.328***	-7.286***	-4.362***
Pack years	0.0281***	-0.00243	-0.00098	-0.549***	0.101**	0.0051	0.00002	-0.0018	0.105**	0.074**
Caucasian ethnicity (ref. Asian)	-0.171	0.0159	0.0121	-3.488	-0.0843	0.0466	-0.0123	0.0029	0.451	0.331
Previous history of lung disease (ref. No)	2.366***	-0.333***	-0.298***	-8.599	2.327	-0.048	-0.148	0.044	-1.276	-1.734*
Married (ref. No)	0.0772	-0.0217	-0.0262	-0.664	-0.912	-0.032	-0.089	0.044*	-0.768	-0.330

*Significant at <.05
**Significant at <.01
***Significant at <.0001

DISCUSSION

To our knowledge, this is one of the few studies which compares the a two-year 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 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 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 risks associated with HTP use when compared to CC use, especially considering the potential indirect effects of CC use on the chronic diseases [12].

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 [13]. 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 [14, 15].

Currently, available research results suggest that HTPs may play a role in harm reduction if smokers completely switch to HTPs from combustible cigarettes. It has been shown that there is less exposure to toxic substances like carbonyls or reactive oxygen species using HTPs [16].

In our previous study we compared 609 CC smokers and 284 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 (25%), 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 use can potentially be less deleterious that continued CC for long-term smokers. 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 more advisable that 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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