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ORIGINAL RESEARCH

Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up

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Background: Health effects of electronic cigarette (EC) use in patients with chronic obstructive pulmonary disease (COPD) are largely unexplored.

Aim: We present findings from a long-term prospective assessment of respiratory parameters in a cohort of COPD patients who ceased or substantially reduced conventional cigarette use with ECs.

Methods: We prospectively re-evaluated COPD exacerbations, spirometric indices, subjective assessments (using the COPD Assessment Tool [CAT] scores), physical activity (measured by the 6-minute walk distance [6MWD]), and conventional cigarette use in EC users with COPD who were retrospectively assessed previously. Baseline measurements prior to switching to EC use were compared to follow-up visits at 12, 24, and 36 months. Age- and sex-matched regularly smoking COPD patients who were not using ECs were included as reference (control) group.

Results: Complete data were available from 44 patients. Compared to baseline in the EC-user group, there was a marked decline in the use of conventional cigarettes. Although there was no change in lung function, significant improvements in COPD exacerbation rates, CAT scores, and 6MWD were observed consistently in the EC user group over the 3-year period ($p<0.01$). Similar findings were noted in COPD EC users who also smoked conventional cigarettes ("dual users").

Conclusion: The present study suggests that EC use may ameliorate objective and subjective COPD outcomes and that the benefits gained may persist long-term. EC use may reverse some of the harm resulting from tobacco smoking in COPD patients.

Keywords: smoking cessation, electronic cigarette, COPD, tobacco harm reduction

Introduction

Smoking is an important cause of avoidable premature mortality globally, mainly due to lung cancer, acute fatal complications of atherosclerotic cardiovascular disease, and chronic obstructive pulmonary disease (COPD).[1,2] COPD is a progressive condition typified by ongoing airway inflammatory and remodeling responses resulting in respiratory symptoms, progressive lung function decline, respiratory failure, cor pulmonale, and death.[3–5] The unique airway inflammatory response in COPD is largely assumed to be due to chronic exposure to a range of smoke toxicants.[6,7]

Stopping conventional tobacco use is the only evidence-based strategy that has been reported to enhance COPD prognosis.[8,9] Prolonged abstinence from smoking attenuates the yearly lung function decline and respiratory symptoms and enhances health status.[10–12] Moreover, smoking cessation decreases the chances of developing and consequently perishing from tobacco-related illnesses.[13]

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Although reducing the negative health burden of tobacco smoking is a clear priority for COPD patients who smoke, high failure rates are frequently reported in these patients.[14,15] Moreover, approved smoking cessation therapies (ie, nicotine replacement therapy, bupropion, and varenicline) only seem to promote modest enduring cessation in smoking COPD patients.[16] This is because the subjects may find it challenging to completely stop using nicotine and/or require longer treatment regimen, support, or nicotine maintenance to possibly aid in attaining continued abstinence from smoking. For these individuals, tobacco harm reduction (THR), that is, the use of combustion-free nicotine delivery systems (ie, electronic cigarettes [ECs]) instead of cigarette smoking, could be a pragmatic compromise with the possibility of significant health gains. Although it is important to acknowledge that nicotine is a potent psycho-stimulant and young people should avoid its use, in conventional cigarettes, it is not nicotine but tobacco combustion chemicals that are the overwhelming cause of tobacco-related disease and death. As respiratory physicians, we should be more concerned of the damage associated with the harmful and potentially harmful constituents generated after combustion than nicotine consumption per se.

The EC has been proposed as a potential THR tool.[17] These products have been rapidly gaining ground over conventional cigarettes due to their efficiency in decreasing tobacco consumption, competitive price, the perception of being a much less harmful smoking alternative and also because they allow the smoker to maintain a "smoking experience without smoking."[18–20] ECs do not contain tobacco, create smoke, or rely on combustion to operate. They are not risk-free, but under normal conditions of use, the level of chemical constituents in their aerosol emissions is substantially lower compared to conventional cigarette smoke.[20–22] Reducing conventional cigarette consumption by switching over to ECs is therefore expected to result in health benefits and may produce substantial health benefits. ECs by providing a much less harmful means to compete with (and even replace) combustible cigarettes may be saving more lives more rapidly than previously possible. Nonetheless, knowledge about the risk–benefit ratio of this strategy, including the use of ECs in smokers with COPD, is scarce.

According to the findings from the 2014 and 2015 National Health Interview Survey, EC use by COPD patients was significant with former smokers with COPD suggesting a reliance on ECs to prevent relapse to tobacco cigarettes.[23] Emerging evidence suggest that COPD smokers who quit or reduce tobacco consumption substantially by switching to EC use are likely to gain significant health benefits. Improvement in respiratory symptoms after switching was reported in 75.7% of 1,190 COPD EC users in a large cross-sectional survey, whereas worsening was reported in only 0.8%.[19]

No negative impact in a retrospective study of COPD smokers who have been "vaping" (the acting of inhaling from ECs) regularly for at least 2 years.[24] Marked attenuation in annual COPD exacerbations and enhanced overall health status (assessed using the COPD Assessment Tool [CAT]) and physical activity (measured by the 6-minute walk distance [6MWD]) were also noted in the same study.[24] However, cross-sectional surveys and retrospective designs cannot establish health effects with certainty.

The aim of the present study was to verify these findings by reporting health outcomes of the third year follow-up in the same cohort of COPD patients who have continued to vape regularly for an additional year.

Methods

Patient population

All the patients in the index study were a cohort of COPD EC users; they were identified from medical records and regularly followed up for a period of 36 months. Another group of age- and sex-matched regularly smoking COPD patients (and not using ECs) was also selected over the same period as a reference (control) group. Details of these patients' populations have been presented elsewhere.[24] COPD diagnosis was made according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria as per the prior published study.[24] In the current study, COPD patients from both the study groups (COPD EC users and COPD controls) were prospectively followed up for an additional 12 months, hence 36 months in total from baseline. The study was approved by the ethics review board of the coordinating center (Policlinico – Vittorio Emanuele Hospitals). We obtained written informed consent from each patient.

Study design and assessments

Details of the study design and assessments have been described previously.[24] Briefly, patients' clinical notes were reviewed three times over 2 years: at baseline (when COPD patients in the EC group first reported EC use), at 12±1.5 months (follow-up visit 1; F/up1), and at 24±2.5 months (follow-up visit 2; F/up2) to acquire details about 1) their respiratory symptoms, 2) smoking status and conventional cigarette consumption per day (cig/day), 3) the number of severe COPD exacerbations in the prior 12 months, 4) post-bronchodilator lung function parameters (forced expiratory flow in 1 second [FEV_1]; forced vital capacity [FVC]; expiratory ratio [FEV_1/FVC]; as well

as the annual rate of FEV_1 decline), 5) CAT scores, and 6) 6MWD.

In the present study, COPD EC users and COPD controls were prospectively re-evaluated for changes in the same objective and subjective parameters at an additional follow-up at 36±3 months (follow-up visit 3; F/up3) compared to baseline. Changes in daily tobacco consumption were chemically confirmed using exhaled breath carbon monoxide (eCO), and EC use were also reviewed. Findings obtained at F/up3 were compared with those from baseline, F/up1 and F/up2. In addition, changes in the relative proportion of COPD GOLD stages over the study period were also evaluated.

Severe exacerbations were defined as respiratory symptoms that necessitated the use of antibiotics and/or oral corticosteroids through the primary care physician, emergency department attendance, and/or admission to hospital. For the latter two, nebulization may have also been administered to improve patient symptoms. CAT is a validated health status questionnaire for use in COPD patients with a 2 unit change considered to be of minimal clinical important difference.[25,26] The 6MWD, which is a test conducted to assess patients' overall ability to conduct daily activities, was only offered to patients who were amenable and physically able to do the test.[27]

Smoking/vaping status

Smoking abstinence was defined as a complete self-reported cessation of tobacco smoking (not even a puff) since the previous study visit. This was also bio-chemically confirmed at F/up3 by eCO levels of ≤7 ppm. COPD EC users in this category are classified as quitters (single users). Patients who used both ECs and conventional cigarettes were classified as dual users.

Analyses

Means (± standard deviation [SD]) and medians (interquartile range [IQR]) were used to express parametric and non-parametric data, respectively. Data for single and dual users was also reviewed. Depending on whether the data were parametric or non-parametric, statistical analyses were conducted using student's *t*-test and Wilcoxon-signed rank test, respectively. Similar statistical analyses were conducted on dual and single users within groups from baseline. Missing data were not considered in the analyses. With repeated parameter measurements over the study period, analysis of repeated measures with Bonferroni correction was conducted for between groups. A two-tailed *p*-value of <0.05 was considered to indicate statistical significance. All statistical evaluations were performed with the Statistical Package for Social Science (SPSS for windows version 18.0; SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Of the 48 COPD patients enrolled in the study at baseline, complete data sets at 36 months were obtained from 44 (37 male and 7 female) patients by the end of the study; data sets from two patients from the EC user group who relapsed to conventional cigarette smoking were not included, and updated clinical notes from two patients from the reference group were not available because one died and the other was lost to follow-up due to relocation. Patients' demographics, objective and subjective parameters, as well as COPD GOLD staging at baseline are summarized in Table 1. No between-group differences were noted at baseline for all the parameters assessed. The patients enrolled had mild-to-severe COPD as per the GOLD guidelines and were managed accordingly.[24]

Smoking consumption and EC use

COPD EC users were characterized by a significant reduction in conventional cigarette use with a mean (±SD) cigarettes/day of 21.9 (±4.5) at baseline falling to 2 (±2.2) at F/up1, 1.6 (±2) at F/up2, and 1.5 (±2.4) at F/up3, respectively ($p<0.001$ for all three visits) (Table 2). No marked changes were observed among COPD controls. In the COPD EC user group, complete abstinence (quitters; exclusive EC users or single users) from daily conventional cigarette consumption was reported in 13/22 (59.1%) EC users at F/up3; tobacco smoking (dual users) in 9/22 (40.9%) (Table 3). A substantial decline in conventional cigarette use was also noted in dual users with the mean (±SD) cigarettes/day at baseline decreasing from 23.9 (±4.9) to 4 (±1.2) at F/up1 to 3.6 (±1.3) at F/up2 and to 3.8 (±1.1) at F/up3, respectively ($p<0.001$ for all three visits) (Table 3). Of note, all the dual users, at all three visits, managed to reduce their conventional cigarette use/day by ≥75% of their baseline consumption. Overall, a statistically significant decrease in conventional cigarettes smoked was consistently observed between the study groups over the 36-month observation period ($p<0.001$).

COPD exacerbations

COPD EC users had a significant diminution in COPD exacerbations; with their mean (±SD) exacerbation rate falling from 2.3 (±0.9) at baseline to 1.7 (±1) at F/up1 ($p=0.002$), 1.4 (±0.9) at F/up2 ($p=0.002$), and 1.3 (±0.9) at F/up3 ($p<0.001$), respectively (Table 2). There were no significant changes in

Table 1 Baseline demographics of study participants (before switching to electronic cigarettes)

Parameter	COPD controls (n=22)	COPD EC users (n=22)	Baseline *p*-value between groups
Age¥	65.2 (±5.6)	66.5 (±6.8)	0.518
Sex	19 M, 3 F	18 M, 4 F	–
COPD GOLD staging			
Stage 1	2	2	–
Stage 2	5	6	–
Stage 3	10	9	–
Stage 4	5	5	–
Post-BD FEV_1* (L)	1.47 (1.17, 1.69)	1.25 (0.97, 1.82)	0.445
Post-BD FVC* (L)	2.34 (2.09, 2.63)	2.49 (2.3, 2.65)	0.787
%FEV_1/FVC¥	59.7 (±7.8)	56.2 (±10.7)	0.221
Pack-years of smoking¥	51.8 (±10.4)	52.2 (±11.1)	0.900
Cig/day¥	20.8 (±4.6)	21.9 (±4.5)	0.221
CAT score*	20 (17.3, 24.8)	21.0 (17.3, 25.0)	0.832
COPD exacerbations¥	2.1 (±1.1)	2.3 (±0.9)	0.657
6MWD* (m)	284.5 (217.5, 365)	289.5 (186.5, 344.8)	0.817

Notes: *Median (interquartile range); ¥mean (± standard deviation).
Abbreviations: 6MWD, 6-minute walk distance; BD, bronchodilator; CAT, COPD Assessment Tool; Cig, conventional cigarettes; COPD, chronic obstructive pulmonary disease; EC, electronic cigarette; F, female; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; M, male.

COPD exacerbation rates over the 3 years in the control group from baseline. A significant (p=0.004) between-group reduction in COPD exacerbations was seen over the 36-month period of the study (Table 2; Figure 1). Consistent reductions in COPD exacerbations were observed in the dual users as well, with their mean (±SD) exacerbation rate of 2.7 (±0.9) at baseline significantly falling to 1.5 (±0.9) at F/up2 (p=0.002) and 1.2 (±0.8) at F/up3 (p=0.001), respectively (Table 3).

Lung function assessments and COPD staging

No significant changes in post-bronchodilator FEV_1 and FVC from baseline were observed over the 36-month period in both the study groups (Table 2; Figure 2A and B). In addition, no overall between study group differences in any spirometric assessments were observed. From baseline to F/up3, there was annual increase of 23.3 mL in FEV_1 observed in the COPD EC user group compared to a decrease of 4.7 mL in the control group (p=0.139).

Changes in GOLD COPD staging are depicted in Figure 3. In the 3-year period, a number of COPD patients in the EC study group down-staged from GOLD COPD Stages 4 and 3 to Stages 3 and 2, respectively. In contrast, there was virtually a lack of change in the COPD GOLD stages in the control group over the observation period.

CAT scores and 6MWD

Subjective COPD assessment, evaluated using CAT scores, improved significantly in the COPD EC group throughout the study ($p \leq 0.01$ for all three visits). Improvements were of clinical relevance with a median CAT score reduction from baseline of 3.5, 3, and 5.5 units at F/up1, F/up2, and F/up3, respectively (Table 2). No significant changes in CAT scores were observed in the control group. Hence, significant (p=0.019) between-group reductions in CAT scores was seen over the 36-month period of the study (Table 2; Figure 4). Consistent and clinically relevant reductions in CAT scores were observed in the dual users as well (Table 3).

Results of 6MWD were available for 13 subjects at F/up1 and F/up2 and for 11 subjects at F/up3 in the COPD EC group; while data from the COPD control group were available for 14 subjects at F/up1 and F/up2 and for 13 subjects at F/up3. Compared to baseline, at 36 months, the 6MWD improved by a median of 70 m (p=0.003) in the COPD EC user group whereas decreased by 7.5 m (p=0.087) in the COPD control group (Table 2). A significant (p=0.001) improvement in 6MWD was seen between study groups over the 36-month period of the study (Table 2).

Discussion

In a cohort of regular EC users with COPD, abstaining from smoking or substantially reducing cigarette consumption ameliorates quality of life as well as respiratory outcomes in COPD and that these positive effects persist long-term. This is in agreement with the notion that quitting smoking is a key strategy not only to prevent the onset of COPD but also to stop its progression into more severe disease stages.[8,10–13] These confirmatory findings are of thoughtful importance

Table 2 Changes in study parameters from baseline at 12-, 24-, and 36-month follow-up visits in COPD controls and COPD EC users

	Baseline	12-month follow-up	Within-group *p*-value vs baseline	24-month follow-up	Within-group *p*-value vs baseline	36-month follow-up	Within-group *p*-value vs baseline	Overall between-group *p*-value from baseline
COPD controls (n=22)								
Post-BD FEV_1* (L)	1.47 (1.17, 1.69)	1.43 (1.15, 1.69)	0.614	1.45 (1.18, 1.64)	0.845	1.47 (1.18, 1.64)	0.697	0.233
Post-BD FVC* (L)	2.34 (2.09, 2.63)	2.30 (2.19, 2.71)	0.094	2.32 (2.17, 2.77)	0.194	2.28 (2.06, 2.57)	0.073	0.077
%FEV_1/FVC	59.7 (±7.8)	58.7 (±7.7)	**0.008**	58.5 (±7.7)	**0.001**	60.2 (±9.3)	0.664	0.454
Cig/day¥	20.8 (±4.6)	20.4 (±3.7)	0.776	20.1 (±5.0)	0.657	19.5 (±3.8)	0.330	<**0.001**
CAT score*	20 (17.3, 24.8)	20 (20, 24.8)	0.162	20 (15.3, 24)	0.512	20 (18, 23.5)	0.662	**0.019**
COPD exacerbations¥	2.1 (±1.1)	2.2 (0.9)	0.740	2.1 (±1.1)	0.825	2.1 (±0.9)	1.000	**0.004**
6MWD*,# (m)	284.5 (217.5, 365)	270 (211, 392)	0.087	277.5 (235, 401.5)	0.133	277 (220.5, 425)	0.087	**0.001**
COPD EC users (n=22)								
Post-BD FEV_1* (L)	1.25 (0.97, 1.82)	1.23 (0.95, 1.76)	0.118	1.29 (0.94, 1.68)	0.173	1.30 (0.99, 1.74)	0.071	
Post-BD FVC* (L)	2.49 (2.3, 2.65)	2.51 (2.0 2.74)	0.101	2.46 (1.92, 2.89)	0.284	2.54 (1.96, 2.88)	0.085	
%FEV_1/FVC¥	56.2 (±10.7)	55.9 (±10.5)	0.470	56.4 (±10.4)	0.693	56.8 (±10.2)	0.480	
Cig/day¥	21.9 (±4.5)	2 (±2.2)	<**0.001**	1.6 (±2)	<**0.001**	1.5 (±2.4)	<**0.001**	
CAT score*	21.0 (17.3, 25.0)	17.5 (16, 20)	<**0.001**	18 (15, 20)	<**0.001**	15.5 (12.5, 23.5)	**0.007**	
COPD exacerbations¥	2.3 (±0.9)	1.7 (±1)	**0.002**	1.4 (±0.9)	**0.002**	1.3 (±0.9)	<**0.001**	
6MWD*,# (m)	289.5 (186.5, 344.8)	310 (218.3, 371.8)	**0.004**	333 (230.3, 374.8)	**0.004**	359.5 (251, 399.8)	**0.003**	

Notes: *Median (interquartile range); ¥mean (± standard deviation). #Thirteen subjects in the COPD EC user group and 14 in the COPD control group at 12- and 24-month review. At 36-month review, 11 subjects in the EC group and 13 subjects in the control group. Values shown in bold are statistically significant.

Abbreviations: COPD, chronic obstructive pulmonary disease; EC, electronic cigarette; n, number; BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; Cig, conventional cigarettes; CAT, COPD Assessment Tool; 6MWD, 6-minute walk distance.

Table 3 Changes in study parameters from baseline at 12-, 24-, and 36-month follow-up visits in single and dual users

Parameters	Baseline	12-month follow-up	Within-group *p*-value vs baseline	24-month follow-up	Within-group *p*-value vs baseline	36-month follow-up	Within-group *p*-value vs baseline
COPD EC users reducing Cig use (dual users)	**(n=9)**	**(n=11)**	**–**	**(n=10)**	**–**	**(n=9)**	**–**
Sex	9 M	10 M, 1 F	–	10 M	–	9 M	–
% smoking reduction compared to baseline	–	82.7 (±4.8)	–	85.1 (±4.7)	–	83.5 (±6.3)	–
Post-BD FEV_1* (L)	0.99 (0.96, 1.84)	1.2 (0.91, 1.7)	**0.026**	1.18 (0.91, 2.01)	0.054	1.25 (0.9, 1.8)	0.132
Post-BD FVC* (L)	2.34 (2.16, 3.13)	2.35 (2.07, 2.89)	0.074	2.52 (2.2, 2.93)	0.162	2.52 (2.2, 2.89)	0.202
%FEV/FVC*	52.1(±9.5)	53.8 (±9.9)	1.000	54.0 (±12.1)	0.863	52.0 (±10)	0.906
Cig/day¥	23.9 (±4.9)	4 (±1.2)	**<0.001**	3.6 (±1.3)	**<0.001**	3.8 (±1.1)	**<0.001**
CAT score*	24 (21, 27)	20 (18, 22)	**<0.001**	19 (16, 22)	**0.005**	20 (14, 25)	**0.022**
COPD exacerbations¥	2.7 (±0.9)	2.3 (±0.8)	0.104	1.5 (±0.9)	**0.002**	1.2 (±0.8)	**0.001**
COPD EC users ceasing Cig use (single users)	**(n=13)**	**(n=11)**		**(n=12)**		**(n=13)**	
Sex	9 M, 4 F	8 M, 3 F		8 M, 4 F		9 M, 4 F	
Smoking reduction compared to baseline	–	–		–		–	
Post-BD FEV_1* (L)	1.32 (1.05, 1.76)	1.26 (1.02, 1.75)	0.886	1.34 (1.14, 1.64)	0.607	1.47 (1.1, 1.65)	0.254
Post-BD FVC* (L)	2.57 (2.01, 2.65)	2.6 (2.7, 2.73)	0.677	2.44 (1.81, 2.83)	0.628	2.55 (1.8, 2.86)	0.277
%FEV/FVC*	59.0 (±10.3)	58 (±11)	0.188	58.4 (±8.8)	0.509	60.1 (±9.3)	0.372
Cig/day¥	20.5 (±3.8)	–		–		–	
CAT score*	18 (17, 24)	16 (15, 18)	**0.002**	16 (15, 19)	**0.004**	14 (12, 20)	**0.018**
COPD exacerbations¥	2.0 (±0.9)	1.2 (±1)	**0.012**	1.3 (±1)	**0.021**	1.3 (±1)	**0.044**

Notes: *Median (interquartile range); ¥mean (± standard deviation). The values shown in bold are statistically significant.

Abbreviations: n, number; COPD, chronic obstructive pulmonary disease; EC, electronic cigarette; M, male; F, female; BD, bronchodilator; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; Cig, conventional cigarettes; CAT, COPD Assessment Tool.

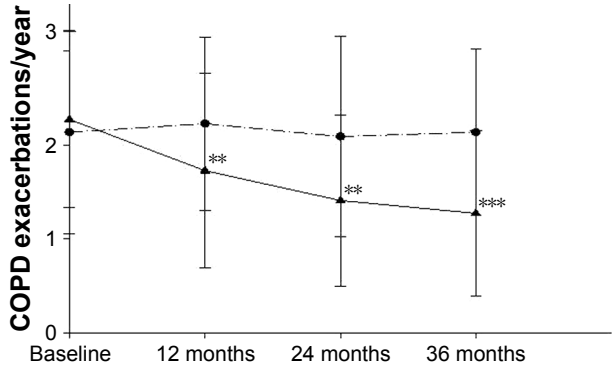

Figure 1 Changes in the number of COPD exacerbations per year from baseline, at follow-up visit 1 (12±1.5 months), visit 2 (24±2.5 months), and visit 3 (36±3 months) separately for COPD EC users (closed triangles) and COPD controls (closed circles). All data are expressed as mean and error bars are standard deviation of the mean. The ** and *** indicate the within-group *p*-value of <0.01 and <0.001, respectively, compared to baseline.
Abbreviations: COPD, chronic obstructive pulmonary disease; EC, electronic cigarette.

as many COPD patients continue their tobacco habit despite their symptoms and show little interest in relinquishing it;[15,16,28] a contradiction that may be justified by the highly addictive disposition of tobacco smoking and the fear of developing depressive symptoms.[28,29]

Over an observation period of ~3 years, only two (8.3%) patients from the COPD EC user group (both were dual users) relapsed to cigarette smoking. Relapse prevention may be another way by which ECs contribute to individual and public health. This is an important consideration, given that smokers with COPD are known to perform poorly in smoking cessation programs due to their high relapse rate.[16,28,29] Perhaps the fact that ECs reproduce the smoking experience and accompanying rituals with large compensatory effect at both physical and behavioral levels may explain the low relapse rates in this study of COPD smokers who switched to ECs. A similar mechanism might explain the low relapse rates observed among smokers not intending to quit[30,31] as well as in smokers with schizophrenia, asthma, and high blood pressure after switching to EC use.[32–34]

This study corroborates previous observations of a lack of worsening in respiratory physiology (post-bronchodilator FEV_1, FVC, and $\%FEV_1/FVC$) in patients with COPD who stopped or considerably reduced their conventional cigarette use by switching to EC use. The absence of marked changes in spirometric indices following smoking cessation is not unusual in COPD smokers and particularly in patients with advanced disease and irreversible airway obstruction[35,36] as is the case in our study population.

The finding that COPD exacerbations were halved in patients who stopped or considerably reduced their smoking habit following switching to ECs was an important finding. This is in agreement with results from two large population studies: one reporting a 43% lower risk COPD-related hospitalizations in previous smokers compared with existing smokers;[37] and the other showing a 22% reduction in COPD exacerbation risk in ex-smokers compared with ongoing smokers when adjusted for comorbidity, COPD severity indices, and socioeconomic status.[38] In contrast, there have also been reports of a lack of any marked differences in hospital admissions between current smokers and ex-smokers with COPD.[39,40] Importantly, these studies did not take into consideration important COPD exacerbation risk

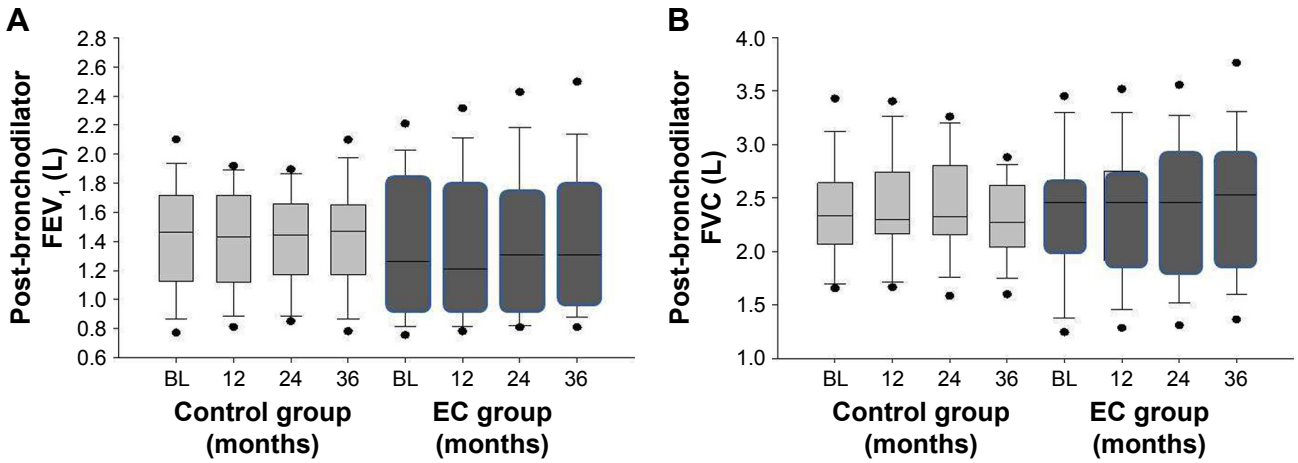

Figure 2 Changes in the FEV_1 (**A**) and FVC (**B**) from baseline, at follow-up visit 1 (12±1.5 months), visit 2 (24±2.5 months), and visit 3 (36±3 months) separately for COPD EC users (dark gray boxes) and COPD controls (light gray boxes). The boxes represent the 25th to 75th percentiles; the line in the boxes indicates the median, and error bars are 5th and 95th percentiles.
Abbreviations: COPD, chronic obstructive pulmonary disease; EC, electronic cigarette; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; BL, baseline.

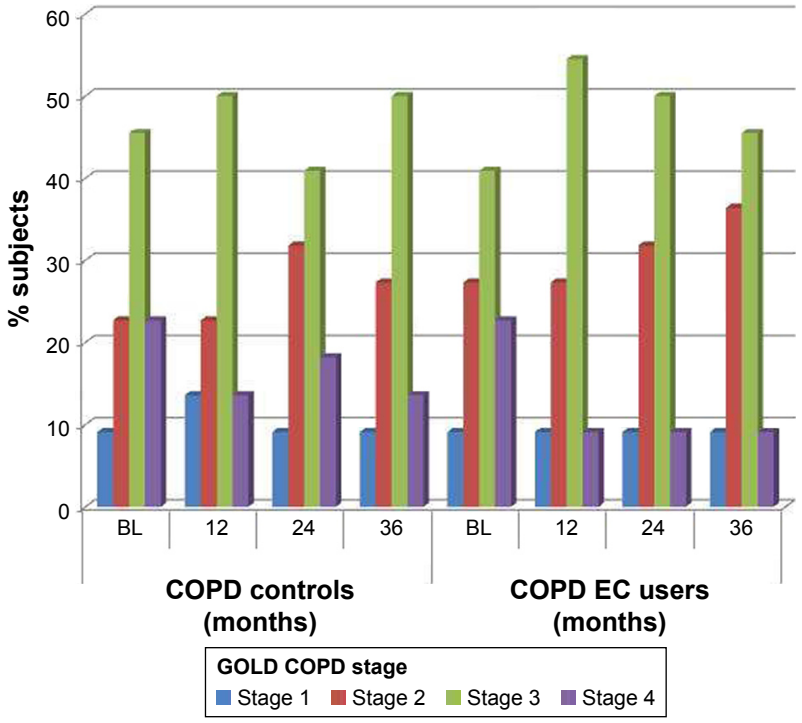

Figure 3 COPD GOLD stage changes over the study period.
Abbreviations: COPD, chronic obstructive pulmonary disease; EC, electronic cigarette; BL, baseline; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

confounders such as smoking abstinence duration, severity of COPD, comorbidities, and age. These confounders were accounted for in the index study. Since chronic exposure to tobacco smoke is known to enhance susceptibility to airway infection,[41,42] it is not surprising that abstention from cigarette smoking by swapping to ECs may result in marked attenuation of respiratory infections and COPD exacerbations.[43]

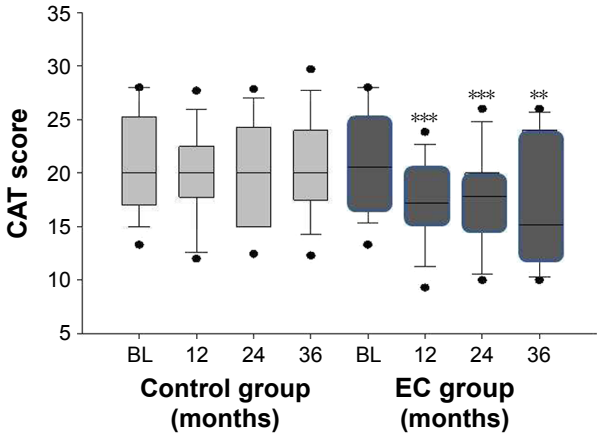

Figure 4 Changes in the CAT scores from baseline, at follow-up visit 1 (12±1.5 months), visit 2 (24±2.5 months), and visit 3 (36±3 months) separately for COPD EC users (dark gray boxes) and COPD controls (light gray boxes). The boxes represent the 25th to 75th percentiles; the lines in the boxes indicate the median, and error bars are 5th and 95th percentiles. The ** and *** indicate the within-group *p*-value of <0.01 and <0.001, respectively, compared to baseline.
Abbreviations: COPD, chronic obstructive pulmonary disease; EC, electronic cigarette; BL, baseline; CAT, COPD Assessment Tool.

Consistent improvements were observed in overall health status and physical activity in our EC-using COPD patient cohort who quit or reduced substantially their conventional cigarette consumption. These clinical changes in CAT and 6MWD confirm our previous observations[24] and are compatible with those reported in undergoing intensive rehabilitation programs in COPD patients.[26,44] The mechanism for these improved health outcomes may be associated with the substantial decline in CO exposure (as well as in carboxyhemoglobin levels) following smoking abstinence[45] and to the linked time-dependent progression in exercise tolerance with abstaining from smoking.[46] Surprisingly, consistent improvements were also observed in dual users. This could be due to the fact that dual users in the index study significantly attenuated their daily smoking by at least 75% (ie, heavy reducers). Also a much larger proportion of less severe COPD GOLD stages patients were dual users, which may have favored the tendency toward harm reversibility.

There are limitations in our observations that need consideration. Our observations are in a small cohort of COPD patients, and hence the results need to be interpreted cautiously. Nonetheless, we observed consistent and clinically significant beneficial effects in several COPD health

indicators. Also, there is the possibility that the patients in the index study may represent a self-selected sample, which may not be representative of all COPD smokers. Another shortcoming is that the 6MWD test was not performed in all study participants, as this was not the standard and some patients declined to do it.

The present study suggests that regular EC use ameliorates several health effect indicators in COPD and demonstrates that these beneficial effects may continue in the longer term. By markedly reducing the number of conventional cigarettes smoked per day and hence exposure to their numerous hazardous toxicants, EC use may not only enhance COPD outcomes, but may also bestow an overall health advantage.[47] Therefore, EC use may be exploited as a less harmful strategy to potentially halt or reverse COPD-related outcomes and, in general, to reduce the risk of smoking-related diseases or the harm from smoking-associated comorbidities. While the sample size in our study was relatively small, the results of this study may provide preliminary evidence that long-term use of ECs is unlikely to result in substantial health concerns in COPD patients. Additional studies in a larger and more diverse sample of COPD EC users are now needed to substantiate and elucidate the emerging role of the e-vapor category for smoking cessation and/or harm reversal in smoking COPD patients.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

In relation to RP's work in the area of tobacco control and respiratory diseases, he has received lecture fees and research funding from Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, MSD, Boehringer Ingelheim, Novartis, Duska Therapeutics, and Forest Laboratories. He has also served as a consultant for Pfizer, Global Health Alliance for Treatment of Tobacco Dependence, CV Therapeutics, NeuroSearch A/S, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, ECITA (Electronic Cigarette Industry Trade Association, in the UK), and Health Diplomat (consulting company that delivers solutions to global health problems with special emphasis on harm minimization). Lecture fees from a number of European EC industry and trade associations (including FIVAPE in France and FIESEL in Italy) were directly donated to vaper advocacy no-profit organizations on the behalf of RP. RP is also currently a scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti-Smoking League) and Head of the European Technical Committee for Standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4). JBM has received honoraria for speaking and financial support to attend meetings/advisory boards from Wyeth, Chiesi, Pfizer, MSD, Boehringer Ingelheim, Teva, GSK/Allen & Hanburys, Napp, Almirall, AstraZeneca, Trudell and Novartis. The authors report no other conflicts of interest in this work.

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