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Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes

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Abstract

Quitting smoking is the most important step smokers can take to improve their health. Nonetheless, there is little information on long-term improvements in lung function and/or respiratory symptoms after smoking cessation. Here we illustrate long-term changes in spirometric indices as well as in respiratory symptoms in smokers invited to quit or reduce their cigarette consumption by switching to electronic cigarettes (ECs). Prospective evaluation of cigarette consumption, spirometry and symptoms was performed in a 1-year randomized controlled trial of smokers receiving EC containing 2.4%, 1.8% or 0% nicotine. Spirometric data are presented on the basis of participants' pooled continuous smoking phenotype classification (Quitters, Reducers, Failures), whereas respiratory symptoms on the basis of their point prevalence-smoking phenotype. Smoking phenotype classification (Quitters, Reducers, Failures) had no significant effect on spirometric indices (FEV_1, FVC and FEV_1/FVC) with the exception of $FEF_{25–75\%}$, which significantly ($P = 0.034$) increased over the time among Quitters; their $FEF_{25–75\%}$ (% predicted) improving from (means $\pm$ S.D.) 85.7 $\pm$ 15.6% at baseline (BL) to 100.8 $\pm$ 14.6%. High prevalence of cough/phlegm (43.1%) and shortness of breath (SoB; 34.8%) was reported at BL with substantial reduction in their frequency at subsequent follow-up visits. These symptoms virtually disappeared very quickly in both quitters and reducers. Smokers invited to switch to ECs who completely abstained from smoking showed steady progressive improvements in their $FEF_{25–75\%}$. Normalization of peripheral airways function was associated with improvement in respiratory symptoms, adding to the notion that abstaining from smoking can reverse tobacco harm in the lung.

Key words: electronic cigarettes, respiratory function tests, respiratory symptoms, smoking cessation, tobacco harm reduction.

INTRODUCTION

Cigarette smoking is the most important cause of avoidable premature mortality in the world and quitting is known to reduce risk of fatal diseases such as lung cancer, acute coronary artery disease, strokes, end-stage chronic obstructive pulmonary disease and other cancers [1]. The World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) encourages abstinence among smokers to reduce health burden associated with combustible tobacco use [2] and smoking cessation drugs are known to increase the likelihood of quitting [3,4].

Chronic exposure to cigarette smoke is associated with a characteristic inflammatory response of the airways, which often leads to progressive decline in lung function [5,6]. Smokers have an accelerated rate of decline in forced expiratory volume in 1 s (FEV_1) [7] and giving up smoking reduces the rate of decline [8]. Quitting smoking is among the most important steps smokers can take to improve their lung health, but there is little information concerning the time-course of improvement in lung function or in respiratory symptoms after smoking cessation in smokers without significant pre-existing lung disease.

Abbreviations: BL, baseline; EC, electronic cigarette; eCO, exhaled carbon monoxide; $FEF_{25–75\%}$, maximum midexpiratory flow; FEV_1, forced expiratort volume in 1 s; FVC, forced vital capacity; SoB, shortness of breath.

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Electronic cigarettes (ECs) are battery-operated devices that simulate the feel and experience of cigarette smoking without burning tobacco [9,10]. Users are predominantly smokers, using them long-term as an alternative for conventional cigarettes, to reduce or quit smoking, to relieve tobacco withdrawal symptoms, and continuing a 'smoking' experience [11,12], but with much reduced health risks [13]. Prospective clinical trials and meta-analyses appear to suggest that ECs can aid smoking cessation and reduction [14–16]. However, there is no information about the long-term lung health effects of ECs use.

Herein we illustrate changes in spirometric indices and respiratory symptoms in association with smoking reduction or abstinence at 12-, 24- and 52-week from participants of the ECLAT study [14] – a prospective 1-year RCT designed to evaluate smoking reduction, smoking abstinence and adverse events in 300 'healthy' smokers switching to ECs. Spirometric measurements and assessment of respiratory symptoms were carried out at baseline (BL) and regularly throughout the study follow-up visits. This provided an opportunity to determine the long-term effects of sustained reduction and abstinence from cigarette smoking on lung function and respiratory symptoms at various times over a 1-year interval in smokers who were invited to quit or reduce their cigarette consumption by switching to ECs.

MATERIALS AND METHODS

Details of participants' characteristics and study design have been previously described [14]. The Ethical Review Board of the 'Policlinico-Vittorio Emanuele' Hospitals approved the study and participants gave written informed consent prior to participation in the study.

Participants

Smokers not intending to quit were invited to switch to first generation cigarette-look-a-like ECs ('Categoria', Arbi Group Srl) as a complete substitute for tobacco smoking. Participants were informed that the purpose of the study was to quantify the impact of reductions in cigarette consumption on lung health and respiratory symptoms by means of regular follow-up visits. No financial incentive was offered for participation.

Inclusion criteria were: (a) smoke$\geqslant$10 tobacco cigarettes per day (cig/day), for at least the past 5 years, (b) age 18–70 years, (c) good general health; (d) not currently attempting to quit smoking or wishing to do so in the next 30 days (this was verified at screening by the answer 'NO' to both questions 'Do you intend to quit in the next 30 days?' and 'Are you interested in taking part in one of our smoking cessation programs?') and (e) committed to follow the trial procedures.

Exclusion criteria were: (a) evidence of airway obstruction as defined by a FEV_1/FVC (forced vital capacity) ratio <0.70; (b) symptomatic cardiovascular and/or doctor diagnosed respiratory disease, psychiatric disorder or major depression; (c) regular medication use; (d) current or past history of alcohol abuse; (e) use of smokeless tobacco or nicotine replacement therapy; and (f) pregnancy or breastfeeding.

Products tested

The 'Categoria' EC (model '401') used in the present study is a rechargeable three-piece design closely resembling a conventional cigarette. Disposable cartridges used in the present study were of three different types, but of identical appearance: 'Original 2.4%' (2.27 ± 0.13% nicotine), 'Categoria 1.8%' (1.71 ± 0.09% nicotine) and 'Original 0%' without nicotine ('sweet tobacco' aroma). The 'Categoria' EC kit and cartridges were provided free of charge by the local distributor (Arbi Group Srl).

Study design

Eligible participants were enrolled into a prospective 1-year three-arms double-blind, controlled, randomized, clinical trial consisting of nine office visits at our smoking cessation clinic (*Centro per la Prevenzione e Cura del Tabagismo – CPCT; Università di Catania, Italy*) to assess biochemically verified (by exhaled carbon monoxide – eCO) cigarette consumption. Participants were randomized into three study arms to receive EC kits with cartridges of identical appearance (12 weeks 'Original 2.4%' – Group A; 6 weeks 'Original 2.4%' and a further 6 weeks 'Categoria 1.8%' – Group B; 12 weeks 'Original 0%' – Group C) using a computer-generated randomization sequence. Spirometry was carried out at BL and at week-12, week-24 and week-52. Self-reported respiratory symptoms in the previous 2 weeks were verified at BL and at each study follow-up visits by asking 4 yes/no questions:

1. Cough/phlegm: '*Do you usually have cough/phlegm in the morning?*'
2. Wheeze: '*Have you heard any wheeze when breathing?*'
3. Shortness of breath: '*Are you ever short of breath?*'
4. Tight chest: '*Have you had difficulty in breathing like a sensation of pressure on your chest?*'

At BL, socio-demographic factors, smoking history, Fagerström Test for Cigarette Dependence scores and eCO levels (Micro CO, Micro Medical) were annotated. Spirometric data and respiratory symptoms were also recorded. Participants received a free EC kit with a full cartridge supply, and were trained on how to use the product. They were told to use the study product ad libitum (up to a maximum of 4 cartridges/day) in the anticipation of reducing cigarette smoking, and to take notes of the daily consumption of conventional cigarettes, cartridge use and adverse events in their study diaries.

Participants were then invited to return to the CPCT at follow-up visits (a) to receive further free cartridge supplies and study diaries for the residual study periods, (b) record their eCO levels, (c) repeat spirometry (at week-12, week-24 and week-52, only), (d) record the presence/absence of respiratory symptoms in the previous 2 weeks, and (e) return completed study diaries and unused study products. By week-12 study visit, no more cartridges were provided, but participants were advised to continue using their ECs if they wish to do so.

Spirometry procedure

Spirometry was conducted according to ATS/ERS guidelines [17]. Prediction values for spirometric indices were the 2012 multi-ethnic reference values for spirometry for the 3–95-year age range by Quanjer et al. [18]. FEV_1, forced vital capacity (FVC), and maximum midexpiratory flow ($FEF_{25–75\%}$) were obtained by using a PC-based electronic spirometer (Micro Medical SpiroUSB ML2525 with Spida 5 software; CareFusion). At least three forced expiratory manoeuvres spaced 1–2 min apart were obtained with subjects sitting comfortably. Measurements were taken late in the morning and participants were asked not to smoke/vape for at least 30 min prior to each visit. A respiratory physician experienced in pulmonary function testing (RP) reviewed spirometry results for quality control. Only technically acceptable tests were used for data analyses. The best FVC and FEV_1 were retained, and $FEF_{25–75\%}$ was selected from the manoeuvre with the largest sum of FEV_1 and FVC. FEV_1/FVC ratio was also computed.

Smoking phenotypes

Smoking abstinence was defined as complete self-reported abstinence from tobacco smoking (not even a puff) since the previous study visit, which was biochemically verified by eCO levels of $\leqslant$7 ppm. Smokers in this category are classified as *Quitters*.

Smoking reduction was defined as sustained self-reported $\geqslant$50% reduction in the number of cig/day from BL (eCO levels were measured to verify smoking status and confirm a reduction compared with BL). Smokers in this category are classified as *Reducers*.

Smokers who were not categorized in the above categories were classified as *Failures*. The study analysed the effects on spirometric indices due to smoking phenotypes, which was defined as consistently maintaining the same phenotype from week-12 to week-52. Thus, the analysis was performed among participants who had a sustained smoking phenotype for at least 40 weeks.

Statistics

Subjects' BL characteristics were compared among products with either 2.4% nicotine (Group A) or 1.8% nicotine (Group B) or no nicotine (Group C). Descriptive data are presented as means $\pm$ standard deviation (S.D.) or medians and interquartile range (IQ) for normally and not normally distributed variables respectively. BL differences among groups (A, B, and C) were investigated by means of one-way analysis of variance (ANOVA) for parametric variables and Kruskal–Wallis test for non-parametric variables. Differences in frequency distribution of categorical variables were evaluated by χ^2 test.

After that BL evaluation was performed, in order to assess the effect of pooled continuous smoking phenotypes (Quitters, Reducers and Failures) on lung function and respiratory symptoms, individual values were compared, irrespective of the study arm that each participant was assigned to. Among these subjects, a Repeated Measures ANOVA model was used: lung function variables at different time points were entered into the model as within factor for assessing spirometric changes with time (four time points: BL, week-12, week-24 and week-52), whereas continuous smoking phenotype was entered as between factor for evaluating its effect on changes.

Differences in frequency of respiratory symptoms at BL, and week-12, week-24 and week-52 were evaluated – irrespective of the study arm that each participant was assigned to – by means of logit hierarchic models (one for each symptom), in which time and smoking phenotype (Quitters, Reducers and Failures) at each time point were the independent variables and the respiratory symptom the dependent one.

The analyses were carried out using Statistical Package for Social Sciences (SPSS) for Windows version 20.0 and P values <0.05 were considered significant.

RESULTS

Participants' characteristics at BL, success rates and adverse events have been reported previously [14]. In brief, after screening 417 subjects, a total of 300 [male 190, female 110; mean ($\pm$S.D.) age of 44.0 ($\pm$12.5) years] smokers (median [IQ range] pack/years of 24.9 [14.0–37.0]) were eligible and consented to participate in the study. BL characteristics were similar among the three study groups (A, B, and C, with the exception of participants' age) including spirometric indices and respiratory symptoms. Two-hundred and twenty-five subjects (75.0%) returned at week-12, 211 (70.3%) at week-24, and 183 (61.0%) for their final follow-up visit at week-52. Smoking reduction and quit rates were not significantly different among study groups: when combining results from study groups A, B and C, smoking reduction was observed in 10.3% of the participants and complete abstinence in 8.7% at week-52 [14]. No serious adverse events occurred during the study.

Complete information on respiratory symptoms was available from 181 participants. Of these, 145 could be categorized as continuous smoking phenotype (either Quitters, or Reducers, or Failures). Among these 145, technically acceptable spirometry data were available at each time point in 130 participants. Their BL characteristics were similar among study groups without significant differences in lung function (Table 1). Similarly, no difference was found at BL in frequency distribution of respiratory symptoms (Table 2).

Given that no difference was found among groups A, B and C, for the purposes of the present study, irrespective of the study arm, BL spirometric and respiratory symptoms data from all study groups were combined together and presented on the basis of their pooled continuous smoking phenotype classification up to week-52 (for spirometric data) and of their point prevalence-smoking phenotype (for respiratory symptoms). BL characteristics were similar among Quitters, Reducers, and Failures for the investigated variables, including lung function (Table 3). The only exception was with respect to cough/phlegm that was significantly more frequent at BL among those resulting quitters (64%) with respect to Reducers (55%) and Failures (36%) (Table 4).

Significant within-subject effect was found for changes in FEV_1, FVC and $FEF_{25–75\%}$ (as percent of predicted) over the time (at BL, and at week-12, week-24 and week-52,

Table 1 **Baseline characteristics of study participants for the overall sample, and separately for each study arm**
Abbreviations: IQR, interquartile range; pack/yrs, pack-years; cig/day, cigarettes smoked per day; eCO, exhaled carbon monoxide; FTND, Fagerström Test of Nicotine Dependence. #χ^2 test; † one-way analysis of variance (ANOVA); ǂ Kruskal–Wallis test.

	Overall sample (No. = 130)	Group A (No. = 46)	Group B (No. = 43)	Group C (No. = 41)	*P* value
Gender (males/females)	75/55	23/23	27/16	25/16	0.48#
Age (years, mean ± S.D.)	42.2 ± 12.6	45.4 ± 13.1	40.5 ± 11.2	40.3 ± 13.0	0.10†
Pack/yr (median [IQR])	24.0 (12.0–35.8)	26.3 (14.6–37.3)	22.5 (13.7–34.8)	24.8 (10.3–35.0)	0.52ǂ
Cig/day (median [IQR])	20.0 (15.0–25.0)	20.0 (15.0–25.0)	18.0 (15.0–20.0)	20.0 (15.8–30.0)	0.26ǂ
eCO (ppm, median [IQR])	20.0 (14.0–28.0)	18.0 (15.0–26.0)	22.0 (17.0–28.0)	19.0 (13.0–29.0)	0.68ǂ
FTND (mean ± S.D.)	5.6 ± 2.2	5.5 ± 2.4	5.5 ± 2.0	5.9 ± 2.0	0.70†
BMI (kg/m^2, mean ± S.D.)	24.3 ± 3.7	24.2 ± 3.1	24.6 ± 4.0	24.1 ± 3.9	0.84†
FEV_1 (l, mean ± S.D.)	3.47 ± 0.81	3.28 ± 0.89	3.61 ± 0.66	3.53 ± 0.85	0.13†
FEV_1 (% predicted, mean ± S.D.)	97.4 ± 11.4	96.1 ± 11.0	97.9 ± 11.4	98.3 ± 12.0	0.66†
FVC (l, mean ± S.D.)	4.33 ± 1.04	4.11 ± 1.11	4.49 ± 0.90	4.42 ± 1.09	0.18†
FVC (% predicted, mean ± S.D.)	98.6 ± 12.2	97.3 ± 12.1	98.8 ± 13.2	100.0 ± 11.6	0.60†
FEV_1/FVC (%, mean ± S.D.)	80.4 ± 5.3	80.0 ± 4.9	80.9 ± 5.9	80.3 ± 5.1	0.71†
$FEF_{25–75\%}$ (l/s, mean ± S.D.)	2.84 ± 0.87	2.67 ± 0.91	2.90 ± 0.77	2.97 ± 0.90	0.25†
$FEF_{25–75\%}$ (% predicted, mean ± S.D.)	80.7 ± 18.2	80.4 ± 16.7	79.1 ± 17.0	82.8 ± 21.0	0.64†

Table 2 **Respiratory symptoms reported at baseline for the overall sample, and separately for each study arm**

	Overall sample (No. = 181)	Group A (No. = 64)	Group B (No. = 63)	Group C (No. = 54)	*P* value (χ^2 test)
Cough/phlegm (yes/no)	78/181 (43.1%)	24/64 (37.5%)	30/63 (47.6%)	24/54 (44.4%)	0.50
Shortness of breath (yes/no)	63/181 (34.8%)	22/64 (34.4%)	22/63 (34.9%)	19/54 (35.2%)	0.99

Table 3 **Baseline characteristics of study participants (No. = 130), separately for each smoking phenotype classification at week-52**
#χ^2 test; † one-way analysis of variance (ANOVA); ǂ Kruskal–Wallis test.

	Failures (No. = 80)	Reducers (No. = 32)	Quitters (No. = 18)	*P* value
Gender (M/F)	41/39	20/12	14/4	0.10#
Age (years, mean ± S.D.)	40.8 ± 12.5	44.1 ± 13.7	44.8 ± 10.5	0.28†
Pack/year (median, IQ range)	24.0 (10.6–34.8)	26.5 (14.6–42.5)	23.0 (16.8–33.6)	0.40ǂ
Cig/day (median, IQ range)	20.0 (15.5–25.0)	19.0 (15.0–30.0)	18.5 (15.0–20.0)	0.28ǂ
eCO (median, IQ range)	22.0 (14.5–29.0)	20.0 (14.5–25.5)	17.0 (12.0–20.0)	0.07ǂ
FTND (mean ± S.D.)	5.9 ± 2.2	5.3 ± 2.0	5.1 ± 2.3	0.24†
BMI (kg/m^2, mean ± S.D.)	24.1 ± 3.5	23.9 ± 3.7	25.7 ± 4.2	0.22†
FEV_1 (l, mean ± S.D.)	3.46 ± 0.84	3.41 ± 0.85	3.62 ± 0.62	0.69†
FEV_1 (% predicted, mean ± S.D.)	96.8 ± 11.9	96.8 ± 10.5	101.1 ± 10.6	0.33†
FVC (l, mean ± S.D.)	4.31 ± 1.04	4.27 ± 1.15	4.51 ± 0.89	0.73†
FVC (% predicted, mean ± S.D.)	98.4 ± 12.7	97.6 ± 11.4	101.3 ± 11.9	0.57†
FEV_1/FVC (%, mean ± S.D.)	80.3 ± 4.8	80.4 ± 6.1	80.7 ± 6.0	0.96†
$FEF_{25–75\%}$ (l/s, mean ± S.D.)	2.88 ± 0.92	2.67 ± 0.83	2.96 ± 0.69	0.41†
$FEF_{25–75\%}$ (% predicted, mean ± S.D.)	80.6 ± 18.2	78.3 ± 19.3	85.7 ± 15.6	0.38†

Table 4 **Baseline characteristics of study participants (No. = 181), separately for each smoking phenotype classification at week-52**

	Failures (No. = 125)	Reducers (No. = 31)	Quitters (No. = 25)	*P* value (χ^2 test)
Cough/phlegm (yes/no)	45/125 (36.0%)	17/31 (54.8%)	16/25 (64.0%)	0.01
Shortness of breath (yes/no)	38/125 (30.4%)	15/31 (48.4%)	10/25 (40.0%)	0.14

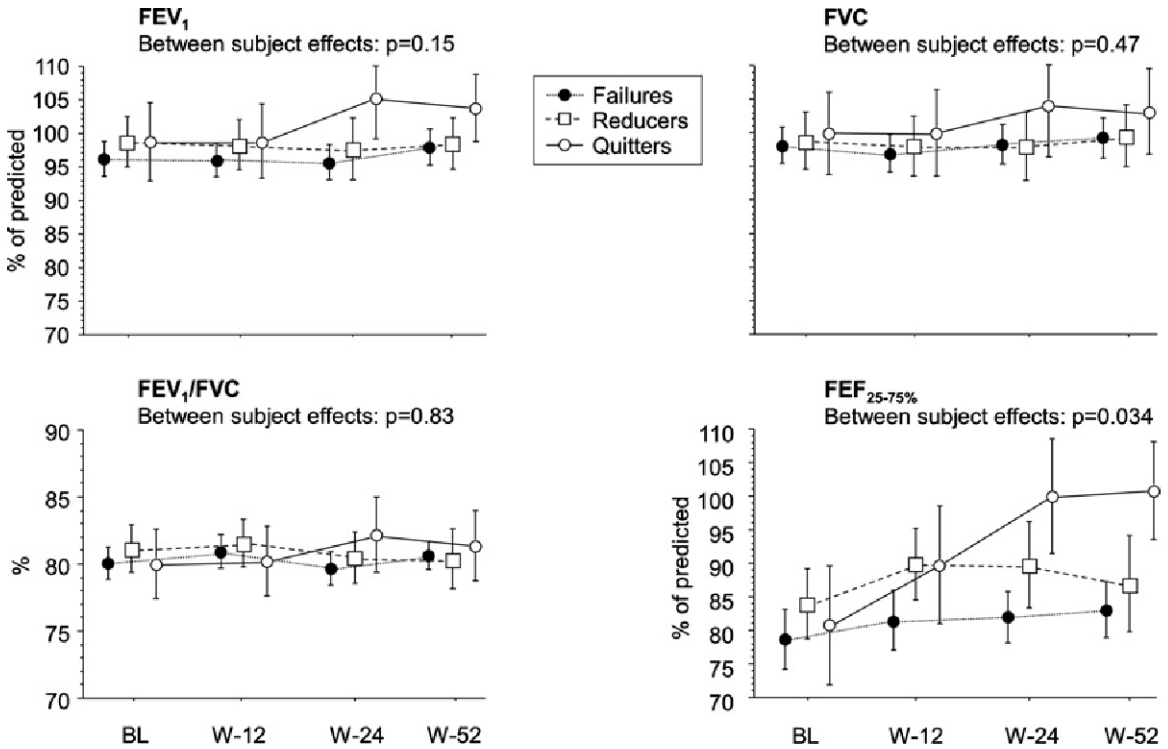

Figure 1 **Means (±95% confidence intervals) of FEV_1, FVC, FEV_1/FVC and $FEF_{25–75\%}$ at baseline (BL) and week-12 (W-12), week-24 (W-24) and week-52 (W-52), separately for smoking phenotype (Failures, Reducers and Quitters)**
For each picture the results of Repeated Measures ANOVA are shown relevant to between subjects effects. Data points refer to 130 subjects with valid spirometric data at all time points. Within subject factor: time. Between subject factor: smoking phenotype.

$P < 0.0001$). Moreover, no effect of smoking phenotype classification (between subject effect) was evident for FEV_1, FVC and FEV_1/FVC. Conversely, an effect of smoking phenotype classification was evident on $FEF_{25–75\%}$ that significantly ($P = 0.034$) increased over the time among Quitters. $FEF_{25–75\%}$ (as percent of predicted) was (means±S.D.) 80.6±18.2, 78.3±19.3 and 85.7±15.6 at BL for failures, reducers and quitters (as per continuous classification at week-52) respectively. The same figures at week-52 were 83.1±18.4, 87.0±20.0 and 100.8±14.6 (Figure 1).

No significant difference in % increase $FEF_{25–75\%}$ (mean±S.D.) was observed in quitters who stopped using EC compared to quitters who were still using EC at any study time point; at week-52, the 19.8% (±15.5) increase from BL in quitters who stopped using EC was not significantly different from the 14.8% (±6.9) increase found in quitters who were still using EC.

Participants in the present study did not report any wheezing or chest tightness. Conversely, high prevalence of cough/phlegm and shortness of breath (SoB) was reported at BL: frequency of cough/phlegm decreased at each follow-up visit with respect to BL regardless of subjects' smoking phenotypes classification (Table 5A). SoB showed a similar behaviour (Table 5B). Symptoms of cough/phlegm and SoB disappeared completely in quitters during the study. The logit hierarchic model demonstrated a significant effect of smoking phenotype on the reduction in cough/phlegm and SoB with time. Changes in the frequency of distribution of cough/phlegm and SoB from BL at week-12, week-24 and week-52 are illustrated in Figure 2. Of note, changes in respiratory symptoms from BL were greater for both reducers and quitters with respect to failures ($P < 0.0001$). The presence/absence of respiratory symptoms at all time-points (BL, week-12, week-24 and week-52) was not associated with significant differences in any of evaluated spirometric variables.

DISCUSSION

This 1-year prospective RCT shows improvements in spirometric indices of peripheral airways as well as in respiratory symptoms in smokers who were invited to quit or reduce their cigarette consumption by switching to first generation ECs. Specifically, the present study shows progressive and consistent improvement in $FEF_{25–75\%}$ among those who completely gave up cigarette smoking. Improvements in $FEF_{25–75\%}$ from BL were no different in quitters who stopped using EC compared with quitters who were still using EC.

One could argue that 'healthy' smokers may not be entirely asymptomatic; yet, from a functional viewpoint, it is unusual to detect airway obstruction on the basis of FEV_1/FVC in smokers without preexisting lung disease [19,20]. Moreover, there is also disagreement about improvements in standard spirometric

Table 5 **Frequency of cough/phlegm (A) and of SoB (B) at baseline and at week-12, week-24 and week-52, separately for each smoking phenotype at relevant time points. The results of the statistical analysis for the effect of smoking phenotype on changes in symptom frequency with time (logit hierarchic model) are reported**
$^{\#}P < 0.0001$ (reference: Failures).

A

	Overall	Failures	Reducers$^{\#}$	Quitters$^{\#}$	Time point
Cough at baseline (*N*, %)	78/181 (43.1%)	38/99 (38.4%)	21/54 (38.9%)	19/28 (67.9%)	Week-12
Cough at week-12 (*N*, %)	33/181 (18.2%)	28/99 (28.3%)	5/54 (9.3%)	0/28 (0%)	
Cough at baseline (*N*, %)	78/181 (43.1%)	40/112 (35.7%)	22/45 (48.9%)	16/24 (66.7%)	Week-24
Cough at week-24 (*N*, %)	26/181 (14.4%)	23/112 (20.5%)	3/45 (6.7%)	0/24 (0%)	
Cough at baseline (*N*, %)	78/181 (43.1%)	45/125 (36.0%)	17/31 (54.8%)	16/25 (64.0%)	Week-52
Cough at week-52 (*N*, %)	28/181 (15.5%)	27/125 (21.6%)	1/31 (3.2%)	0/25 (0%)	

B

	Overall	Failures	Reducers$^{\#}$	Quitters$^{\#}$	Time point
SoB at baseline (*N*, %)	63/181 (34.8%)	30/99 (30.3%)	20/54 (37.0%)	13/28 (46.4%)	Week-12
SoB at week-12 (*N*, %)	5/181 (2.8%)	5/99 (5.1%)	0/54 (0%)	0/28 (0%)	
SoB at baseline (*N*, %)	63/181 (34.8%)	31/112 (27.7%)	20/45 (44.4%)	12/24 (50.0%)	Week-24
SoB at week-24 (*N*, %)	4/181 (2.2%)	4/112 (3.6%)	0/45 (0%)	0/24 (0%)	
SoB at baseline (*N*, %)	63/181 (34.8%)	38/125 (30.4%)	15/31 (48.4%)	10/25 (40.0%)	Week-52
SoB at week-52 (*N*, %)	5/181 (2.8%)	5/125 (4.0%)	0/31 (0%)	0/25 (0%)	

indices (e.g., FEV_1, FVC) after smoking cessation even in smokers with COPD or asthma [21–23]. After excluding subjects with a $FEV_1/FVC < 0.70$, we did not find any evidence of airways obstruction at any of the subsequent follow-ups, irrespective of participants' continuous smoking phenotype classification. This is not unexpected, given that we did not include smokers with known preexisting diagnosis of lung disease.

However, highly sensitive respiratory functional tests can detect early airflow limitation of more peripheral airways in 'healthy' smokers, where standard spirometric measurements are insensitive to lung structural change. Ventilation distribution tests have been explored with success for early detection of dysfunction of more peripheral airways in smokers without spirometric evidence of airway obstruction [24,25]. These isolated abnormalities in small airway function can be partly reversed after smoking cessation with recovery already occurring after 1 week and with constant improvement for up to 8 months [25,26]. The findings of the present study are in line with these observations: significant positive changes in $FEF_{25–75\%}$ from BL were already detected at 3 months after switching in those who completely gave up tobacco smoking, with steady progressive improvements being also present at 6 and 12 months. In this population, smoke-induced dysfunction of more peripheral airways appears fully reversible. The volume-dependence of $FEF_{25–75\%}$ may possibly limit its reliability in measures repeated over the time: in fact, due to increase in FVC, $FEF_{25–75\%}$ could decrease [27]. Nevertheless, in the present study, we recorded a slight and not significant increase in FVC among Quitters over the time, whereas $FEF_{25–75\%}$ significantly increased. Thus, we are confident that possible FVC changes did not affect our results.

Our findings are also in agreement with the progressive improvements in $FEF_{25–75\%}$ observed in asthmatic smokers who quit smoking after switching to regular ECs use [28]. The explanation for the improvement in $FEF_{25–75\%}$ is unknown, but probably relates to the progressive reversal of the pro-inflammatory effects of cigarette smoke on the peripheral airways in those who quit smoking [19]. This was also suggested in 1972 by McFadden and Linden [29] who found that $FEF_{25–75\%}$ increased after cessation of smoking possibly due to the existence of reversible structural changes in the peripheral airways of smokers. By contrast, reversal of peripheral airways obstruction measured by $FEF_{25–75\%}$ was not observed in participants who kept on smoking or in those reducing tobacco consumption. Although this is expected in smoking failures, findings from the Lung Health Study reveal improved lung function in a subset of smokers with early COPD who substantially reduced (>85% reduction) their cigarette consumption [30]. However, in the present study only subjects without any evidence of airway obstruction at BL were included. These findings are also in agreement with the consistent improvements in lung function observed in asthmatic smokers who greatly reduced smoking (from 22.4 cig/day at BL to 3.9 cig/day at follow-up) after switching to regular ECs use [28]. Given that the cumulative cigarette consumption (i.e., pack/years) was similar at BL across smoking phenotypes, a possible explanation for the lack of $FEF_{25–75\%}$ reversal in the study participants who reduced tobacco consumption is that a low level in cigarette reduction – by sustaining compensatory smoking – was unlikely to significantly attenuate the structural damage of cigarette smoke.

High prevalence of cough/phlegm (43.1%) and SoB (34.8%) was reported at BL. The self-reported prevalence of cough/phlegm is in agreement with those from smokers in the general population [reviewed in 19], but the high proportion of SoB can be also explained by the phrasing in the question 'Are you ever short of breath?' that does not distinguish between SoB with very strenuous activity and SoB with moderate activity.

Study participants invited to quit or reduce their cigarette consumption by switching to ECs reported fast substantial improvements of these symptoms from BL. In particular, symptoms

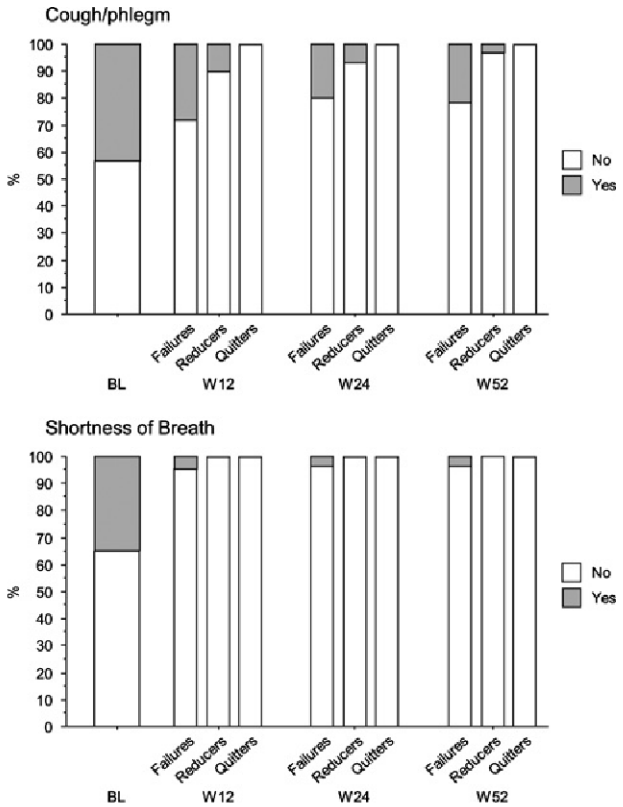

Figure 2 Changes in frequency distribution (percent of 181 subjects with complete respiratory symptom information) of cough/phlegm (upper panel) and SoB (lower panel)

Differences among smoking phenotypes are shown at week-12, week-24 and week-52. A logit hierarchic model demonstrated a significant ($P < 0.0001$) greater effect among Reducers and Quitters on the reduction in cough/phlegm and SoB with respect to Failures.

of cough/phlegm and SoB virtually disappeared in both quitters and reducers. Comparable improvements have been shown in longitudinal studies, with cough/phlegm decreasing within 1–2 months after smoking cessation [31,32]. However, the effect of smoking cessation on SoB in smokers from general populations is less clear, with at least two studies showing no difference in the prevalence of SoB after cessation [32,33]. Differences in study designs and study populations (e.g., our participants were younger, had less cumulative exposure to cigarette smoke, had no airway obstruction, and did not report clinically significant post-cessation weight gain after switching to EC in the present study [unpublished data]) may explain why the prompt resolution of SoB in our study participants was not present in other studies. It must be noticed also that Failures presented a reduction in symptoms from enrolment to week-52. Namely, among Failures, cough moved from 36% to 22% and SoB from 30% to 4%, even though these changes were to a lesser extent with respect to Reducers and Quitters. This could be attributed to the Failures' persistence in the study [34] with an e-cigarette use comparable to that of Quitters. Regularly attending follow-up visits might well have had an effect in recalling of symptoms. However, to our knowledge, validated measures for symptoms and symptom severity are not available for subjects with simple bronchitis: in fact, none of the enrolled subjects had a doctor diagnosis of respiratory disease.

Although we acknowledge that it is misleading to imply a causal relationship, the mechanism for the observed long-term improvements in respiratory symptoms following smoking cessation might be related to the reversal of pathological and inflammatory changes in the lung induced by smoking in the first place. In a separate analysis of the same study, we have shown that, by substantially reducing daily cigarette consumption and exposure to their harmful toxicants, it is possible to obtain steady progressive normalization of inflammatory biomarkers in the exhaled breath of smokers invited to switch to ECs [35]. In particular, for cough/phlegm, the most obvious change appears to be associated with a reduction in goblet cell hyperplasia in the airways [36], consistent with an attenuation in mucus hypersecretion and cough. Considering the substantial reduction in CO (as well as in COHb levels) upon cessation in the present study [14], the prompt resolution of SoB may be consistent with a parallel increase in exercise tolerance.

Our study is the first to investigate the long-term effects of sustained smoking reduction and abstinence on spirometric indices in smokers who were invited to switch to ECs. It has the advantage of an interventional prospective trial approach, which minimizes the possibility of reverse causality of case–control and cross-sectional studies; smoking abstinence was biochemically verified at each study visit; the effects of specific continuous smoking phenotypes were investigated on serial spirograms from the same smokers over several time points for up to one year.

There are however some limitations. Firstly, participants may represent a self-selected sample (e.g. smokers not intending to quit switching to ECs), possibly not representative of all smokers quitting or reducing tobacco smoking. Secondly, findings are likely to be product specific and cannot be generalized to other ECs on the market. Thirdly, the use of a continuous smoking phenotype classification, the exclusion of technically unacceptable spirograms and the absence of financial incentive to study participants, may have contributed to high attrition rates in our study and to small sample size in some smoking phenotype subgroup cohorts. Therefore, results should be interpreted with caution. Nonetheless, in spite of the limited sample size, the improvement in $FEF_{25–75\%}$ was significant and consistent throughout the study. Lastly, assessment of symptoms may be liable to recall bias and should be considered with prudence.

By substantially reducing daily cigarette consumption and exposure to their harmful toxicants, we have shown steady progressive normalization of peripheral airways function, which was also associated with an overall improvement in respiratory symptoms in smokers who were invited to switch to ECs. Similar improvements were observed in quitters who stopped using EC and in quitters who were still using EC. These findings, together with emerging evidence in ECs users with preexisting airways disease, add to the notion that EC use can reverse harm from tobacco smoking in the lung [37]. Larger and longer prospective studies will be required to confirm whether normalization of peripheral airways function in smokers abstaining from tobacco consumption can translate into efficient prevention of COPD.

CLINICAL PERSPECTIVES

- Although larger long-term studies are warranted to confirm potential health benefits in smokers who switch from tobacco to e-cigarettes, the emerging evidence suggests that abstaining from smoking by using e-cigarettes can reverse harm from tobacco smoking.
- Doctors are asking for reliable and accurate information on respiratory health in regular e-cigarette users.
- The evidence-based notion that substitution of conventional cigarettes with e-cigarettes is unlikely to raise significant health concerns and can lead to improvements in respiratory outcomes, can improve counseling between physicians and their respiratory patients using or intending to use e-cigarettes.

AUTHOR CONTRIBUTION

Fabio Cibella and Pasquale Caponnetto contributed to data analysis and interpretation, participated in drafting the manuscript, approved the present final version, and accounted for the accuracy and integrity of the work. Davide Campagna, Maria Domenica Amaradio, Massimo Caruso and Cristina Russo contributed to data acquisition, critically revised the manuscript, approved the present final version, and accounted for the accuracy and integrity of the work. Donald Cockcroft and Riccardo Polosa contributed to data interpretation, participated in critical revision of the manuscript, approved the present final version, and accounted for the accuracy and integrity of the work.

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COMPETING INTERESTS

R.P. has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has also served as a consultant for Pfizer and Arbi Group Srl, an Italian distributor of e-Cigarettes. R.P. is currently scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian acronym for 'Italian Anti Smoking League'). F.C., D.C., P.C., M.D.A., M.C., C.R. and D.W.C. have no relevant conflict of interest to declare in relation to this work.

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REFERENCES

1 http://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/tobacco_related_mortality/index.htm (accessed April 2016)
2 World Health Organization (2003), WHO Framework Convention on Tobacco Control. ISBN: 9241591013
3 Polosa, R., Benowitz, N.L. (2011) Treatment of nicotine addiction: present therapeutic options and pipeline developments. Trends Pharmacol. Sci. **32**, 281–289 CrossRef PubMed
4 Caponnetto, P., Russo, C. and Polosa, R. (2012) Smoking cessation: present status and future perspectives. Curr. Opin. Pharmacol. **12**, 229–237 CrossRef PubMed
5 MacNee, W. (2005) Pathogenesis of chronic obstructive pulmonary disease. Proc. Am. Thorac. Soc. **2**, 258–266 CrossRef PubMed
6 Morjaria, J.B., Malerba, M. and Polosa, R. (2010) Biologic and pharmacologic therapies in clinical development for the inflammatory response in COPD. Drug Discov. Today **15**, 396–405 CrossRef PubMed
7 Fletcher, C., Peto, R., Tinker, C. and Speizer, F.E. (1976) The Natural History of Bronchitis and Emphysema., Oxford University Press, New York
8 Willemse, B.W., Postma, D.S., Timens, W. and Ten Hacken, N.H.T. (2004) The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. Eur. Respir. J. **23**, 464–476 CrossRef PubMed
9 Caponnetto, P., Campagna, D., Papale, G., Russo, C. and Polosa, R. (2012) The emerging phenomenon of electronic cigarettes. Expert Rev. Respir. Med. **6**, 63–74 CrossRef PubMed
10 Caponnetto, P., Russo, C., Bruno, C.M., Alamo, A., Amaradio, M.D. and Polosa, R. (2013) Electronic cigarette: a possible substitute for cigarette dependence. Monaldi Arch. Chest. Dis. **79**, 12–19 PubMed
11 Farsalinos, K.E., Romagna, G., Tsiapras, D., Kyrzopoulos, S. and Voudris, V. (2014) Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. Int. J. Environ. Res. Public Health **11**, 4356–4373 CrossRef PubMed
12 Farsalinos, K.E., Romagna, G., Tsiapras, D., Kyrzopoulos, S. and Voudris, V. (2013) Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. Subst. Abuse **7**, 139–146 PubMed
13 Farsalinos, K.E. and Polosa, R. (2014) Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarettes substitutes: a systematic review. Ther. Adv. Drug Safety **5**, 67–86 CrossRef
14 Caponnetto, P., Campagna, D., Cibella, F., Morjaria, J.B., Caruso, M., Russo, C. and Polosa, R. (2013) Efficiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. PLoS One **8**, e66317 CrossRef PubMed
15 Rahman, M.A., Hann, H., Wilson, A., Mnatzaganian, G. and Worrall-Carter, L. (2015) E-cigarettes and smoking cessation: evidence from a systematic review and meta-analysis. PLoS One **10**, e0122544 CrossRef PubMed
16 Polosa, R., Morjaria, J.B., Caponnetto, P., Campagna, D., Russo, C., Alamo, A., Amaradio, M. and Fisichella, A. (2014) Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study. Intern. Emerg. Med. **9**, 537–546 CrossRef PubMed
17 Miller, M.R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., Crapo, R., Enright, P., van der Grinten, C.P., Gustafsson, P. et al. (2005) ATS/ERS Task Force. Standardisation of spirometry. Eur. Respir. J. **26**, 319–338 CrossRef PubMed

18 Quanjer, P.H., Stanojevic, S., Cole, T.J., Baur, X., Hall, G.L., Culver, B.H., Enright, P.L., Hankinson, J.L., Ip, M.S., Zheng, J. et al. (2012) Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur. Respir. J. **40**, 1324–1343 CrossRef PubMed

19 Willemse, B.W., Postma, D.S., Timens, W. and ten Hacken, N.H. (2004) The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. Eur. Respir. J. **23**, 464–476 CrossRef PubMed

20 Lee, P.N. and Fry, J.S. (2010) Systematic review of the evidence relating FEV1 decline to giving up smoking. BMC Med. **8**, 84 CrossRef PubMed

21 Scanlon, P.D., Connett, J.E., Waller, L.A., Altose, M.D., Bailey, W.C., Buist, A.S., Tashkin, D.P., Lung Health Study Research Group (2000) Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. Lung Health Study. Am. J. Respir. Crit. Care Med. **161**, 381–390 CrossRef

22 Tashkin, D.P., Rennard, S., Taylor Hays, J., Lawrence, D., Marton, J.P. and Lee, T.C. (2011) Lung function and respiratory symptoms in a 1-year randomized smoking cessation trial of varenicline in COPD patients. Respir. Med. **105**, 1682–1690 CrossRef PubMed

23 Polosa, R. and Thomson, N.C. (2013) Smoking and asthma: dangerous liaisons. Eur. Respir. J. **41**, 716–726 CrossRef PubMed

24 Verbanck, S., Schuermans, D., Meysman, M., Paiva, M. and Vincken, W. (2004) Noninvasive assessment of airway alterations in smokers: the small airways revisited. Am. J. Respir. Crit. Care Med. **170**, 414–419 CrossRef PubMed

25 Buist, A.S., Nagy, J.M. and Sexton, G.J. (1979) The effect of smoking cessation on pulmonary function: a 30-month follow-up of two smoking cessation clinics. Am. Rev. Respir. Dis. **120**, 953–957 PubMed

26 Verbanck, S., Schuermans, D., Paiva, M., Meysman, M. and Vincken, W. (2006) Small airway function improvement after smoking cessation in smokers without airway obstruction. Am. J. Respir. Crit. Care Med. **174**, 853–857 CrossRef PubMed

27 Cockcroft, D.W. and Berscheid, B.A. (1980) Volume adjustment of maximal midexpiratory flow. Importance of changes in total lung capacity. Chest **78**, 595–600 CrossRef PubMed

28 Polosa, R., Morjaria, J., Caponnetto, P., Caruso, M., Strano, S., Battaglia, E. and Russo, C. (2014) Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal. Int. J. Environ. Res. Public Health **11**, 4965–4977 CrossRef PubMed

29 McFadden, Jr, E.R. and Linden, D.A. (1972) A reduction in maximum mid-expiratory flow rate. A spirographic manifestation of small airway disease. Am. J. Med. **52**, 725–737 CrossRef PubMed

30 Simmons, M.S., Connett, J.E., Nides, M.A., Lindgren, P.G., Kleerup, E.C., Murray, R.P., Bjornson, W.M. and Tashkin, D.P. (2005) Smoking reduction and the rate of decline in FEV(1): results from the Lung Health Study. Eur. Respir. J. **25**, 1011–1017 CrossRef PubMed

31 Buist, A.S., Sexton, G.J., Nagy, J.M. and Ross, B.B. (1976) The effect of smoking cessation and modification on lung function, Am. Rev. Respir. Dis. **114**, 115–122

32 Tashkin, D.P., Clark, V.A., Coulson, A.H., Simmons, M., Bourque, L.B., Reems, C., Detels, R., Sayre, J.W. and Rokaw, S.N. (1984) The UCLA population studies of chronic obstructive respiratory disease. VIII. Effects of smoking cessation on lung function: a prospective study of a free-living population. Am. Rev. Respir. Dis. **130**, 707–715 PubMed

33 Krzyzanowski, M., Robbins, D.R. and Lebowitz, M.D. (1993) Smoking cessation and changes in respiratory symptoms in two populations followed for 13 years. Int. J. Epidemiol. **22**, 666–673 CrossRef PubMed

34 Cramer, J.A., Roy, A., Burrell, A., Fairchild, C.J., Fuldeore, M.J., Ollendorf, D.A. and Wong, P.K. (2008) Medication compliance and persistence: terminology and definitions. Value Health **11**, 44–47 CrossRef PubMed

35 Campagna, D., Cibella, F., Caponnetto, P., Amaradio, M.D., Caruso, M., Morjaria, J.B., Malerba, M. and Polosa, R Changes in breathomics from a 1-year randomized smoking cessation trial of electronic cigarettes. Eur. J. Clin. Invest, in the press

36 Mullen, J.B., Wright, J.L., Wiggs, B.R., Paré, P.D. and Hogg, J.C. (1987) Structure of central airways in current smokers and ex-smokers with and without mucus hypersecretion: relationship to lung function. Thorax **42**, 843–848 CrossRef PubMed

37 Polosa, R. (2016) Electronic cigarette use and harm reversal: emerging evidence in the lung. BMC Med. **13**, 54 CrossRef

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