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Lung function and respiratory symptoms in a 1-year randomized smoking cessation trial of varenicline in COPD patients

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Summary
There are few data concerning changes in lung function and respiratory symptoms in smokers with chronic obstructive pulmonary disease (COPD) weeks to months after quitting smoking. We examined serial changes in spirometry and Clinical COPD Questionnaire (CCQ) scores (measuring respiratory symptoms and health-related quality of life) in COPD participants by smoking status during a smoking cessation trial.

In this randomized, double-blind trial, smokers with mild-to-moderate COPD were treated with varenicline 1 mg b.i.d. or placebo for 12 weeks and followed to Week 52. Primary endpoints of abstinence were previously reported. Secondary endpoints were mean changes from baseline in post-bronchodilator forced expired volume in 1 s (FEV_1) and CCQ scores.

Change from baseline in post-bronchodilator FEV_1 was significantly improved in continuous abstainers (121.8 mL) *vs.* continuous smokers (37.9 mL) at Week 12 ($P = 0.0069$), but not at Weeks 24 or 52. Mean change from baseline at Week 12 in CCQ Total Score was significantly better in continuous abstainers (−1.04) *vs.* continuous smokers (−0.53; $P < 0.0001$): this improvement was sustained at Weeks 24 and 52.

In a 1-year cessation trial of smokers with COPD, continuous abstinence compared with continuous smoking significantly improved post-bronchodilator FEV_1 at Week 12 (although the difference narrowed subsequently) and CCQ Total Scores at Week 12, with sustained improvement thereafter.

(Trial registry: http://www.clinicaltrials.gov; trial identifier: NCT00285012)

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Introduction

Smoking cessation is the most important strategy for reducing the accelerated rate of decline in lung function[1–3] and for improving respiratory symptoms in smokers with chronic obstructive pulmonary disease (COPD).[4] In the Lung Health Study, as well as slowing age-related decline in forced expired volume in 1 s (FEV_1), smoking cessation was also associated with an absolute improvement in FEV_1 among sustained quitters (participants who were biochemically validated as abstinent at every annual visit) 1 year after enrolment.[2,3] However, there is little information concerning the time course of improvement in lung function or in respiratory symptoms and health-related quality of life (QoL) among COPD patients at earlier time points in the year following smoking cessation. Such information could be useful for informing smokers with COPD regarding how soon the benefits of smoking cessation could be expected after successful quitting.

Since the Lung Health Study demonstrated a significant improvement in lung function and respiratory symptoms in sustained quitters assessed beginning no earlier than 1 year after study entry,[2–4] we examined spirometric indices, as well as respiratory symptoms and health-related QoL, in association with smoking and abstinence at earlier times during the 1-year study period of a randomized, placebo-controlled clinical trial of varenicline—a pharmacotherapy for smoking cessation—in 504 smokers with spirometrically-confirmed mild-to-moderate COPD.[5] Spirometry was administered at baseline and at 12, 24 and 52 weeks following randomization, and a respiratory QoL questionnaire was administered at baseline and regularly during the treatment and follow-up periods. This provided an opportunity to determine the effects of sustained abstinence from smoking on lung function, respiratory symptoms and health status at various times over a 1-year interval following smoking cessation in patients with COPD.

Materials and methods

Participants

Participants were smokers ($\geq$10 cigarettes per day) motivated to quit, with mild-to-moderate COPD (post-bronchodilator FEV_1/forced vital capacity [FVC] $<$70% and FEV_1% predicted $\geq$50%). Participants who used systemic corticosteroids or those who had been treated or hospitalized for a COPD exacerbation during the 4-week period prior to screening were excluded. Other exclusion criteria have been published previously[5] and are listed in Supplemental Table 1. The study was approved by the institutional review board at each site, and participants provided written informed consent. The study was conducted in compliance with the Declaration of Helsinki[6] and the International Conference on Harmonization Good Clinical Practices Guidelines.[7]

Study design

The study was conducted from May 2006 to April 2009.[5] This was a randomized, double-blind, multinational, 27-centre study in which participants with mild-to-moderate COPD received varenicline 1 mg b.i.d. or placebo for 12 weeks (titrated during Week 1), followed by 40 weeks of non-treatment follow-up.[5] Participants were randomized to varenicline or placebo in a 1:1 ratio using a block randomization procedure with investigative site as the stratification variable. Investigators obtained subject randomization numbers and treatment group assignments through a central web-based, or telephone call-in drug management system or through instruction from the sponsor. At the baseline visits, eligible participants received a smoking cessation self-help booklet and $\leq$10 min of counselling. The target quit date (TQD) coincided with the Week 1 visit. Counselling ($\leq$10 min) was provided at clinic visits (weekly from Weeks 1—13, then at Weeks 16, 24, 32, 40, 48 and 52) and by telephone 3 days after the TQD and then in Weeks 14, 20, 28, 36 and 44.

Spirometry was performed before and 30—45 min after the administration of 200 μg albuterol or salbutamol at screening, at baseline and at Weeks 12, 24 and 52, or at early termination visits. Spirometry was performed after any residual bronchodilation from the last dose of COPD medication was expected to have dissipated; participants had been instructed not to take any COPD medication, including inhaled bronchodilators, for the appropriate times before the study visit. Spirometry techniques followed the American Thoracic Society and European Respiratory Society Task Force 2005 Guidelines.[8] The spirometer was required to print the results from at least the three best manoeuvres (numeric results, volume-time graphs and flow-volume graphs). Before any study participants were tested, certification of each study site required evidence of a 3.00 L calibration check demonstrating better than 3% spirometer volume accuracy. The pre- and post-bronchodilator spirometry tests from the first five participant visits were faxed to a central reviewer (P Enright, University of Arizona, Tucson, USA) who graded (A—F) the quality of the FEV_1 and the FVC, as was carried out for the Lung Health Study.[9] Site and technologist certification was awarded when at least 80% of the quality grades were A or B. Whenever possible, the same spirometry technologist tested each participant for the duration of the study. A central review of the quality of the 10 most recent spirometry tests was initiated in June 2008 (around the time of final visits).

At each clinic visit throughout the study, participants completed the Clinical COPD Questionnaire (CCQ; ©2003 Van der Molen et al.),[10] a 10-question instrument using a 6-point Likert scale to assess the symptoms and health status of patients with COPD over the past week.[10] Items on the CCQ are divided into the following domains: Respiratory Symptoms (*e.g.* shortness of breath, cough and phlegm production [4 questions]), Functional State (*e.g.* ability to climb stairs, carry out housework, dress/wash self or visit friends etc. [4 questions]) and Mental State (level of concern about getting a cold or feeling down due to breathing problems [2 questions]) related to their COPD. The Total Score (average of the 10 questions above) can be used to assess the effect of the disease on the QoL of the individual.

Efficacy and safety evaluations

The primary endpoint of the trial was carbon monoxide (CO)-confirmed continuous abstinence rate (CAR) for Weeks

9—12 (last 4 weeks of treatment) and the key secondary endpoint was CAR for Weeks 9—52. Adverse events (AEs) were recorded and followed up until resolution or stabilization occurred to a level acceptable to the investigator and sponsor. Other secondary endpoints, reported herein, were change from baseline in post- and pre-bronchodilator FEV_1 and in the total score, as well as the individual domain scores, for the CCQ at Weeks 12, 24 and 52.

Statistical analysis

The sample size for the study of 500 randomized participants was estimated to provide at least 99% power to detect a difference in Week 9—12 CAR between the varenicline and placebo groups based on an odds ratio (OR) of 2.79 and a placebo rate of 18%.[5] This sample size was estimated to also provide at least 81% power to detect a difference in Week 9—52 CAR based on an OR of 2.21 and a placebo rate of 9%.[5]

Post hoc subgroup analyses were performed with respect to observed smoking status pattern at three time periods: Weeks 9—12, 9—24 and 9—52. Since smoking status was based on post-baseline data collected during active treatment, the loss of randomization imposed limitations on the interpretability of comparative smoking status results. At each visit, abstinence was defined as a CO-confirmed response of "no smoking since last visit". A subject was considered to be a continuous abstainer (or a continuous smoker) if, for *every* visit in the respective time period, he

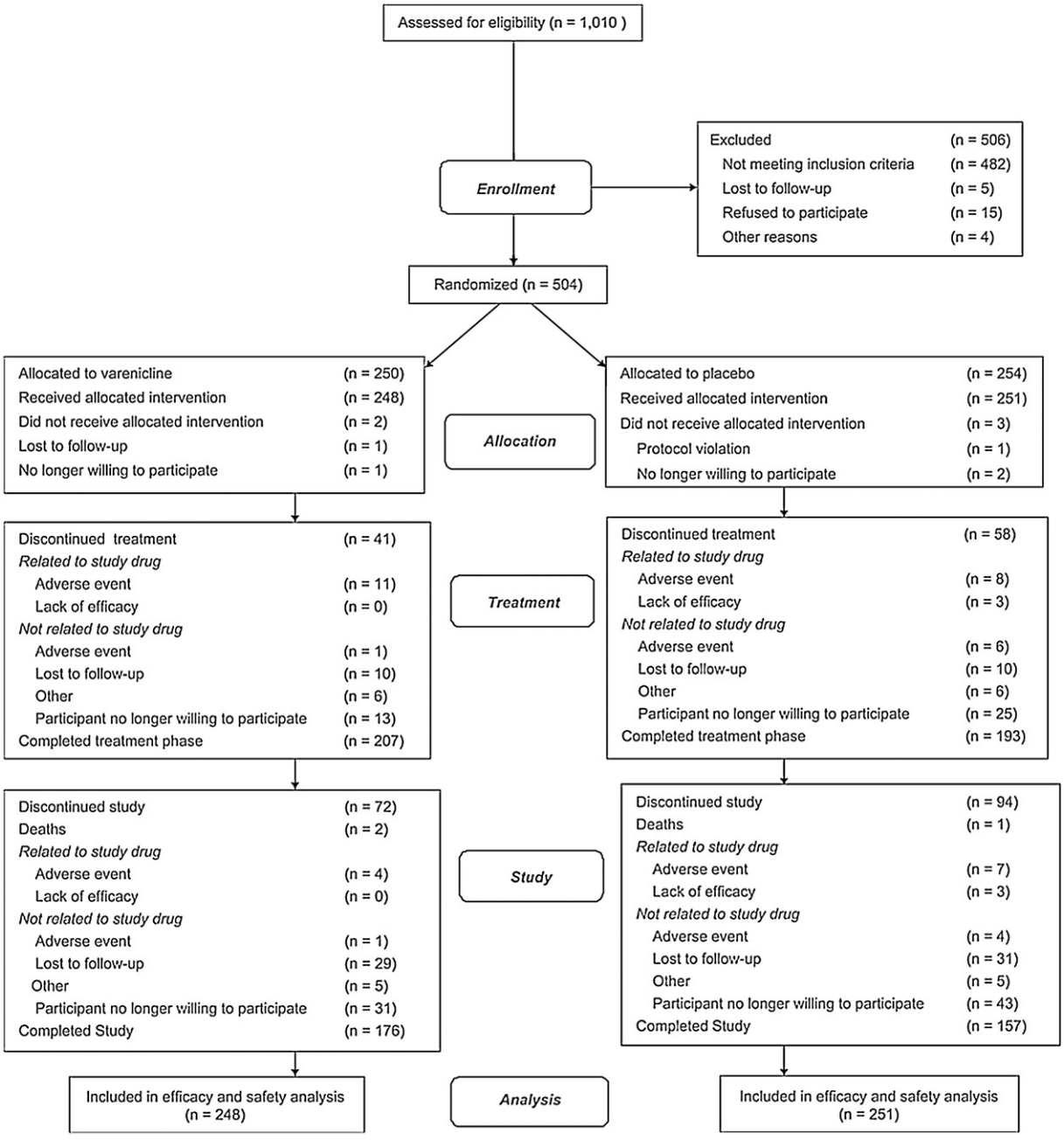

Figure 1 Participant disposition. Reproduced with permission from Ref. [5].

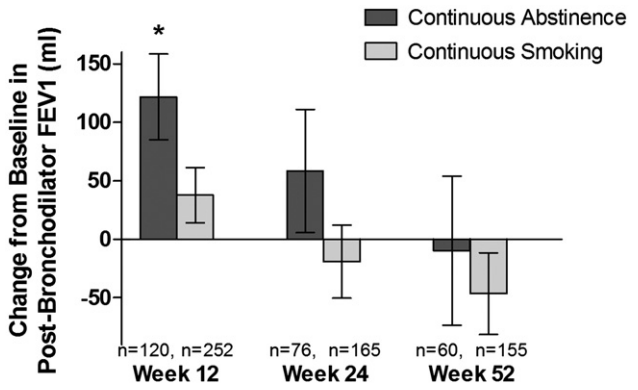

Figure 2 Changes from baseline in post-bronchodilator forced expired volume in 1 s (FEV_1) at Weeks 12, 24 and 52 (least-squares means with adjusted 95% confidence intervals) by smoking status (continuous abstinence *vs*. continuous smoking during Weeks 9—12, 9—24 and 9—52, respectively). *Indicates $P < 0.05$ for difference between continuous abstinence *vs*. continuous smoking.

or she was deemed abstinent (or not abstinent, respectively). Participants not meeting either criterion were not included in the subgroup analysis for that time period.

Changes from baseline in post- and pre-bronchodilator FEV_1 were analyzed via an analysis of covariance (ANCOVA) model consisting of baseline FEV_1, with smoking status, pooled centre and their interaction, conducted separately for each of the three time periods. Least-squares (LS) means were presented by smoking status, with associated individual 95% confidence intervals (CIs), adjusted to aid the correct interpretation of overlapping intervals.[11]

The CCQ was analyzed with respect to Total Score as well as separately for each of the three domains (Respiratory Symptoms, Functional State and Mental State). Change from baseline in CCQ score was analyzed via an ANCOVA model consisting of baseline CCQ score, with smoking status, pooled centre and their interaction, conducted separately for each of the three time periods with graphical presentation of LS means summaries.

Results

Full results for patient disposition, baseline smoking characteristics, CARs and AEs have been reported previously[5] and here we report a summary of those findings.

Disposition

Briefly, 250 and 254 participants were randomized to the varenicline and placebo treatment groups, respectively (Fig. 1). Of these, 207 and 193, respectively, completed the 12-week treatment phase; and 176 and 157, respectively, completed the study.[5]

Baseline characteristics

In summary, participants had a mean age of 57.1 years, were mainly male (62.3%) and Caucasian (83%), smoked an average of 40.5 pack-years and 24.4 cigarettes/day and had a mean Fagerström Test for Nicotine Dependence score of 6.1, a mean baseline post-bronchodilator FEV_1 of 69.9% predicted and Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I (21.9%), II (66.8%) and III (11.2%) severity; GOLD stage III participants were randomized and studied in violation of the entry criteria.[5]

Continuous abstinence rates

Varenicline ($N = 248$) *vs*. placebo ($N = 251$) CARs were 42.3% and 8.8%, respectively, (OR 8.40 [95% CI 4.99—14.14]) for Weeks 9—12 ($P < 0.001$), 25.8% and 7.2%, respectively, (OR 4.88 [95% CI 2.75—8.65]) for Weeks 9—24 ($P < 0.001$) and 18.6% and 5.6%, respectively, (OR 4.04 [95% CI 2.13—7.67]) for Weeks 9—52 ($P < 0.001$).[5]

Spirometry

Nearly all sites demonstrated good quality test sessions for more than 8 of 10 final visits. The LS mean change from baseline in post-bronchodilator FEV_1 was significantly improved ($P = 0.0069$) in the continuous abstainers of Weeks 9—12 (121.8 mL) *vs*. continuous smokers of Weeks 9—12 (37.9 mL) (Fig. 2; Table 1). However, statistical significance was not achieved for the Weeks 9—24 smoking status comparison ($P = 0.0700$) nor for Weeks 9—52 ($P = 0.4654$). The LS mean change from baseline in pre-bronchodilator FEV_1 was not significantly different at any time point (Table 2).

Clinical COPD Questionnaire (CCQ)

The LS means of CCQ Total Score showed significantly greater improvement from baseline at Week 12 in the

Table 1 Changes from baseline in post-bronchodilator forced expired volume in 1 s (FEV_1) at Weeks 12, 24 and 52 (least-squares means with adjusted 95% CIs) by smoking status (continuous abstinence *vs*. continuous smoking during Weeks 9—12, 9—24 and 9—52, respectively).

	Continuous Abstinence[a]			Continuous Smoking[a]			ANCOVA
	n	LS Mean	Adjusted 95% CI	*n*	LS Mean	Adjusted 95% CI	*P* value[b]
Week 12	120	121.8	85.0, 158.5	252	37.9	14.0, 61.9	0.0069
Week 24	76	58.4	5.7, 111.0	165	−19.1	−50.3, 12.1	0.0700
Week 52	60	−9.6	−73.4, 54.1	155	−46.3	−81.3, −11.4	0.4654

[a] Based on Weeks 9—12 for Week 12 results, Weeks 9—24 for Week 24 results and Weeks 9—52 for Week 52 results.
[b] Model included baseline FEV_1, pooled centre, smoking status and pooled centre by smoking status interaction. Note that when comparing the number of participants between Tables 1, 2 and 3 that there are some missing values on ≥1 more of the measures.
LS: least squares; CI: confidence interval; ANCOVA: analysis of covariance.

Table 2 Changes from baseline in pre-bronchodilator forced expired volume in 1 s (FEV_1) at Weeks 12, 24 and 52 (least-squares means with adjusted 95% CIs) by smoking status (continuous abstinence *vs.* continuous smoking during Weeks 9—12, 9—24 and 9—52, respectively).

	Continuous Abstinence[a]			Continuous Smoking[a]			ANCOVA
	n	LS Mean	Adjusted 95% CI	*n*	LS Mean	Adjusted 95% CI	*P* value[b]
Week 12	124	54.8	13.5, 96.2	261	7.0	−20.1, 34.0	0.1696
Week 24	78	−25.2	−95.5, 45.1	179	7.4	−33.4, 48.1	0.5642
Week 52	60	−38.7	−99.6, 22.2	156	−101.8	−135.2, −68.4	0.1890

[a] Based on Weeks 9—12 for Week 12 results, Weeks 9—24 for Week 24 results and Weeks 9—52 for Week 52 results.
[b] Model included baseline FEV_1, pooled centre, smoking status and pooled centre by smoking status interaction. Note that when comparing the number of participants between Tables 1, 2 and 3 that there are some missing values on ≥1 of the measures. LS: least squares; CI: confidence interval; ANCOVA: analysis of covariance.

continuous abstainers *vs.* the continuing smokers, and this significantly greater improvement was sustained at Weeks 24 and 52 (Fig. 3A; Table 3). Furthermore, a significant difference in improvement from baseline at Weeks 12, 24 and 52 was also observed in all three CCQ domain scores (Respiratory Symptom score, Functional State score and Mental State score) in the corresponding Weeks 9—12, 9—24 and 9—52 continuous abstinence subgroups as compared with the respective continuing smoker subgroups (Fig. 3B—D; Table 3).

Adverse events

Briefly, AEs occurred in 183 (73.8%) participants receiving varenicline and 164 (65.3%) receiving placebo. Serious AEs were infrequent in both groups and were not considered treatment-related. Three participants died (two varenicline-group participants and one placebo-group participant); however, no deaths were considered treatment-related.[5] The most frequent AEs occurring in the varenicline group were nausea (27.0% *vs.* 8.0%), abnormal dreams (10.9% *vs.* 2.8%), upper respiratory tract infection (9.7% *vs.* 8.4%), insomnia (9.7% *vs.* 6.0%), flatulence (7.3% *vs.* 5.2%) and vomiting (6.5% *vs.* 2.4%).[5]

Discussion

Varenicline showed superior efficacy with respect to CARs compared with placebo at the end of treatment (Weeks 9—12) and at the end of the non-treatment follow-up period (Weeks 9—52), findings comparable to those previously obtained with varenicline in smokers in general.[12,13] While a significant improvement in post-bronchodilator FEV_1 from baseline was noted at 12 weeks in continuous abstainers *vs.* continuous smokers, the change in mean post-bronchodilator FEV_1 measurements diminished over time such that the continuous abstainers had mean post-bronchodilator FEV_1 scores comparable to continuous smokers when followed up to 1 year. The reasons for the subsequent apparent diminution in the effect of quitting and continuous abstinence from smoking on lung function change that was observed at 12 weeks are unclear and unexpected, although it should be noted that the study was not powered to detect statistically significant differences in lung function.

These lung function findings at 1 year after quitting smoking and remaining abstinent are in contrast to the results of the Lung Health Study in which a statistically significant mean increase in FEV_1 (47 mL or 1.98% predicted) was noted at 1 year among the 840 participants who were abstinent at 1 year compared with a 49 mL (0.74% predicted) decrease in FEV_1 in the continuing smokers.[3] Although spirometry was performed at 4 months among the Special Intervention group of the Lung Health Study (those who received intensive counselling in addition to nicotine replacement therapy), these lung function data have not been analyzed or reported by smoking status. In a smoking cessation study conducted in 370 patients with COPD (mean FEV_1 55.8% predicted) using nicotine sublingual tablets and behavioural support, 113 completed the trial with 1-year follow-up, of whom 36 were successful sustained abstainers at 1 year.[14] Among sustained abstainers, at 1 year FEV_1 improved by 60 mL ($P = 0.048$), compared with a decrease of 161 mL in the 31 participants who continued to smoke without any reduction in smoking amount, and a decrease of 5 mL in the 46 participants who continued to smoke but reduced their daily smoking to <7 cigarettes or by at least 50%.[14] Post-baseline spirometry data were not reported at earlier time points than 1 year during this study. Thus, the 1-year results of the Lung Health Study[3] and a smaller study[14] are at variance with the findings from the present study. The reasons for these differences are unclear. It is also unclear whether a greater improvement in lung function might have occurred in the former studies at earlier time points following successful smoking cessation with a subsequent diminution in this effect over the remainder of the first year after quitting, as was found in the present study. While several studies have shown a decrease in the age-related decline in lung function with smoking cessation over a period of 2—21 years among smokers with chronic airflow obstruction, as reviewed by Willemse et al.,[15] to our knowledge there are little published data on the short-term changes in lung function over the weeks to months after quitting smoking and remaining abstinent.

The CCQ is a validated 10-item self-administered QoL questionnaire that measures Respiratory Symptoms, Functional State and Mental State in patients with COPD.[10] The CCQ Total Score in patients with GOLD stages I—III has shown significant correlations with the St. George's Respiratory Questionnaire (SGRQ; $\rho = 0.67$ to $\rho = 0.72$), as well

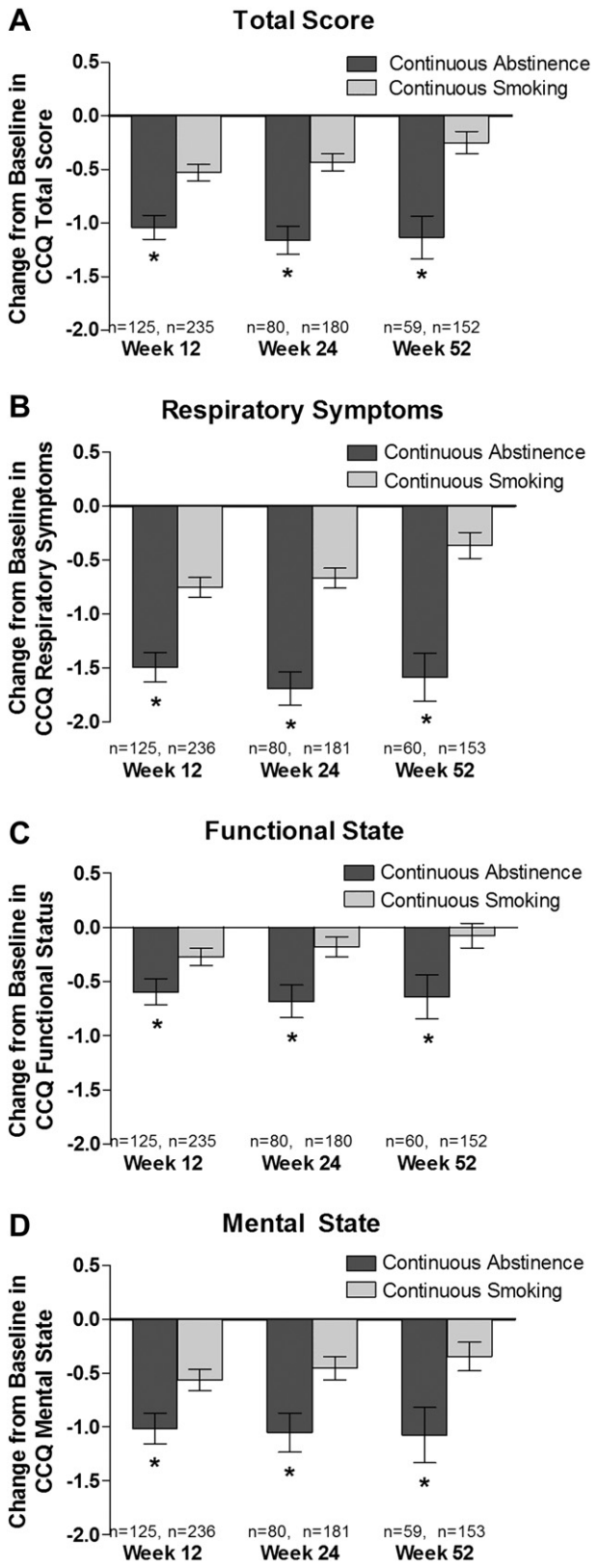

Figure 3 Changes from baseline in Clinical COPD Questionnaire (CCQ) scores for the (A) Total Score and individual CCQ domain scores of (B) Respiratory Symptoms, (C) Functional Status and (D) Mental State at Weeks 12, 24 and 52 (least-squares means with adjusted 95% confidence intervals) by smoking status (continuous abstinence *vs.* continuous smoking during Weeks 9–12, 9–24 and 9–52, respectively). *Indicates $P < 0.05$ for difference between continuous abstinence *vs.* continuous smoking.

as with FEV_1% predicted ($\rho = -0.49$).[10] The CCQ has also been shown to be equally reliable and valid when compared with the self-reported Chronic Respiratory Questionnaire (CRQ-SR) in patients with COPD.[16] In the present study, sustained quitting was associated with improvements in QoL in participants with mild-to-moderate COPD, as demonstrated by the fact that the continuously abstinent participants showed significantly greater improvements than the continuous smokers in each of the domains of the CCQ (Respiratory Symptoms, Functional State and Mental State), as well as in the mean Total Score changes from baseline (Fig. 3A–D; Table 3). The disparity between the comparatively sustained benefits of continuous abstinence from smoking with respect to improvement in respiratory symptoms and QoL compared with the disappointingly diminishing benefits observed with spirometry suggests that the symptomatic improvement was probably related, in large part, to factors other than improvement in spirometric indices, possibly including a reduction in hyperinflation that was not assessed in this study.

While a number of non-randomized studies have shown beneficial effects of smoking cessation on respiratory symptoms in smokers in general,[17] few longitudinal studies are available regarding the effect of smoking cessation on respiratory symptoms in smokers with COPD. The largest such study was the Lung Health Study, in which dyspnoea, cough $\geq$3 months/year and phlegm $\geq$3 months/year were present in 42–44%, 49–51% and 42–43%, respectively, of participants in the different smoking intervention groups at baseline.[4] The change in prevalence of respiratory symptoms from baseline was assessed annually with the first post-baseline assessment having been performed at the first annual visit. Most of the change in the prevalence of symptoms occurred during the first year of follow-up: the sustained quitters showing the greatest decline and the continuing smokers the least decline, with little change over the remaining 4 years of the 5-year trial. Results for chronic cough, sputum production and shortness of breath were very similar to one another. Unlike the present study, however, the impact of changes in smoking habits on respiratory symptoms was not assessed at earlier time points than 1 year following smoking cessation. In a much smaller smoking cessation study in COPD patients, significant improvements in SGRQ total and domain scores from baseline to 1 year were noted in the 36 continuous abstainers: −10.9 (95% CI −15.5, −6.4) for Total Score; −28.6 (95% CI: −35.4, −21.7) for symptoms score; −6.3 (95% CI −12.1, −0.6) for activity score; and −8.0 (95% CI −12.6, −3.5) for impact score.[14] These results are consistent with the findings from the present study of significant improvements in QoL in continuous abstainers at 1 year.

In a randomized, controlled trial of behavioural counselling for smoking cessation in participants with mild-to-moderate COPD, mean changes in baseline total and domain scores for the CCQ were assessed among those who

Table 3 Changes from baseline in Clinical COPD Questionnaire (CCQ) scores for the Total Score and individual CCQ domain scores (Respiratory Symptoms, Functional Status and Mental State) at Weeks 12, 24 and 52 (least-squares means with adjusted 95% CIs) by smoking status (continuous abstinence *vs*. continuous smoking during Weeks 9—12, 9—24 and 9—52, respectively).

CCQ	Change from Baseline to:	Continuous Abstinence[a]			Continuous Smoking[a]			ANCOVA
		n	LS Mean	Adjusted 95% CI	*n*	LS Mean	Adjusted 95% CI	*P* value[b]
Total Score	Week 12	125	−1.04	−1.15, −0.93	235	−0.53	−0.60, −0.45	<0.0001
	Week 24	80	−1.16	−1.29, −1.03	180	−0.43	−0.51, −0.35	<0.0001
	Week 52	59	−1.13	−1.33, −0.93	152	−0.25	−0.35, −0.15	<0.0001
Respiratory Symptoms	Week 12	125	−1.50	−1.63, −1.36	236	−0.75	−0.85, −0.66	<0.0001
	Week 24	80	−1.69	−1.85, −1.54	181	−0.67	−0.76, −0.58	<0.0001
	Week 52	60	−1.59	−1.81, −1.37	153	−0.37	−0.49, −0.24	<0.0001
Functional Status	Week 12	125	−0.60	−0.71, −0.48	235	−0.27	−0.35, −0.19	0.0015
	Week 24	80	−0.68	−0.83, −0.53	180	−0.18	−0.27, −0.09	<0.0001
	Week 52	60	−0.64	−0.85, −0.44	152	−0.08	−0.19, 0.04	0.0006
Mental State	Week 12	125	−1.02	−1.16, −0.87	236	−0.57	−0.66, −0.47	0.0002
	Week 24	80	−1.05	−1.23, −0.87	181	−0.45	−0.56, −0.35	<0.0001
	Week 52	59	−1.07	−1.33, −0.82	153	−0.34	−0.48, −0.21	0.0003

[a] Based on Weeks 9—12 for Week 12 results, Weeks 9—24 for Week 24 results and Weeks 9—52 for Week 52 results.
[b] Model included baseline response value, pooled centre, smoking status and pooled centre by smoking status interaction. Note that when comparing the number of participants between Tables 1, 2 and 3 that there are some missing values on ≥1 of the measures.
LS: least squares; CI: confidence interval; ANCOVA: analysis of covariance.

had prolonged abstinence from smoking at 26 weeks (n = 62—67, depending on domain) and those with prolonged abstinence at 52 weeks (n = 28—30, depending on domain).[16] The results demonstrated statistically significant improvements in the total and symptom scores for the CCQ at 26 weeks that were maintained at 52 weeks, indicating that the improvements in respiratory symptoms and QoL following smoking cessation are durable.

While the mechanism for the improvements in lung function and respiratory symptoms following smoking cessation in patients with COPD is most likely related to at least a partial reversal of pathological and inflammatory changes in the lung that had been induced by smoking in the first place, only a few studies, mostly cross-sectional, provide information relating to possible effects of smoking cessation on lung pathology and inflammation, as reviewed by Willemse et al.[15] The most obvious change appears to be a reduction in goblet cell hyperplasia in central airways (although not in peripheral airways),[18] consistent with a reduction in mucus hypersecretion and symptoms of chronic bronchitis. From cross-sectional studies conducted in current and ex-smokers with COPD, it does not appear that structural changes other than goblet cell hyperplasia reverse after smoking cessation.[15] It is more likely that the slowing of the accelerated decline in FEV_1 following smoking cessation in patients with COPD is due to a reduction of inflammation, although changes in the levels of various inflammatory cells, their products, proinflammatory cytokines or their soluble receptors in blood have been variable,[15] possibly related in part to confounding by inhaled corticosteroid therapy. Cross-sectional studies evaluating bronchial biopsies and lung tissue from smokers and ex-smokers with COPD have shown either a decrease in or persistence of lung inflammation after smoking cessation,[19—22] although prospective studies conducted mainly in smokers without chronic respiratory symptoms or airflow obstruction using sputum, bronchoalveolar lavage fluid and/or blood have more consistently shown a reduction in inflammation with smoking cessation[23—26] or smoking reduction.[27]

In summary, analysis of serial spirometric data from the varenicline COPD study demonstrates significant short-term (12-week) improvements in lung function following smoking cessation with continuous abstinence from 9 to 12 weeks, but these short-term improvements were not sustained at 24 or 52 weeks in those who remained continuously abstinent. Although the reason for this diminution of the early improvements in lung function are unclear, it is possible that significant long-term improvements may not be evident until a further extended period of abstinence from smoking in excess of 1 year has been achieved. On the other hand, stopping smoking and maintaining abstinence resulted in an improvement in respiratory symptoms and QoL that was not only evident at 12 weeks but also persisted for as long as 52 weeks. The longer persistence of the benefits of sustained smoking cessation for respiratory symptoms than for lung function change suggests that the symptomatic improvement could not be entirely attributed to spirometric improvement. Findings from this study provide evidence of respiratory benefits of smoking cessation in COPD patients that can be perceived in the short-term and may therefore be useful in motivating smokers with COPD to quit.

Conflict of Interest Statements

Dr. Tashkin has received fees for serving as a consultant and/or speaker for the following pharmaceutical companies: Pfizer; Boehringer-Ingelheim; AstraZeneca; GlaxoSmithKline; Dey Labs; Sepracor (now Sunovion); and Novartis. Dr. Tashkin has also received grant support from Pfizer, Boehringer-Ingelheim, AstraZeneca, GlaxoSmithKline, Dey Labs, Novartis, Sepracor, Osiris Therapeutics and Chiesi.

Dr. Rennard has consulted or participated in advisory boards for: ABIM, Adelphi Research, Almirall/Forest, APT, AstraZeneca, Boehringer-Ingelheim/Pfizer, BoomCom, Capital Research, CommonHealth, Decision Resources, Easton Associates, Equinox, Forest (Cory Paeth), Fulcrum, Gerson Lehman, GSK Eclipse, Guidepoint, Informed, Insyght, MedImmune, Novartis, Oriel, Pearl, Pfizer (varenicline), PharmaVentures, Prescott, Propagate Pulmonary Reviews, Roche, Schering Plough, Smith Research, Talecris, UBC. Dr Rennard has given lectures for: American College of Osteopathic Physicians, Asan Medical Center, American Thoracic Society, COPD Foundation, Creative Education Concepts, Duke, Information TV, Nycomed, Otsuka, University of Washington, University of Alabama-Birmingham. Dr Rennard has received industry-sponsored grants from: AstraZeneca, Otsuka, Pfizer, Nabi, Merck.

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Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.rmed.2011.04.016.

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