ARTHRITIS & RHEUMATOLOGY
Vol. 70, No. 11, November 2018, pp 1829–1834
DOI 10.1002/art.40557

BRIEF REPORT

Smoking in Systemic Sclerosis: A Longitudinal European Scleroderma Trials and Research Group Study

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Objective. **Data on the role of tobacco exposure in systemic sclerosis (SSc; scleroderma) severity and progression are scarce. We aimed to assess the effects of smoking on the evolution of pulmonary and skin manifestations, based on the European Scleroderma Trials and Research group database.**

Methods. **Adult SSc patients with data on smoking history and a 12–24-month follow-up visit were included. Associations of severity and progression of organ involvement with smoking history and the Comprehensive Smoking Index were assessed using multivariable regression analyses.**

Results. **A total of 3,319 patients were included (mean age 57 years, 85% female); 66% were never smokers, 23% were ex-smokers, and 11% were current smokers. Current smokers had a lower percentage of antitopoisomerase autoantibodies than previous or never smokers (31% versus 40% and 45%, respectively). Never smokers had a higher baseline forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio than previous and current smokers ($P < 0.001$). The FEV_1/FVC ratio declined faster in current smokers than in never smokers ($P = 0.05$) or ex-smokers ($P = 0.01$). The baseline modified Rodnan skin thickness score (MRSS) and the MRSS decline were comparable across smoking groups. Although heavy smoking (>25 pack-years) increased the odds of digital ulcers by almost 50%, there was no robust adverse association of smoking with digital ulcer development.**

Conclusion. **The known adverse effect of smoking on bronchial airways and alveoli is also observed in SSc patients; however, robust adverse effects of smoking on the progression of SSc-specific pulmonary or cutaneous manifestations were not observed.**

Systemic sclerosis (SSc; scleroderma) is a rare, multisystem autoimmune disorder (1). Hypoxia and oxidative stress have been implicated in the pathophysiology of its generalized microangiopathy and fibrosis (1). Although smoking does not appear to confer a risk for SSc development (2), it has vasoconstrictive effects and increases free-radical exposure, and together with other proinflammatory and immunomodulatory effects may exacerbate SSc manifestations (3). Data on the role of tobacco exposure with regard to the severity of SSc organ manifestations and progression are, however, scarce, and at times contradictory (4). A Canadian cohort study of 606 patients, for example, demonstrated an increased frequency of digital ulcers

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Submitted for publication January 19, 2018; accepted in revised form May 10, 2018.

(DUs) in smokers (4), whereas a study of 172 Australian patients showed no association of smoking history with vascular characteristics (5).

Larger studies and robust data assessing the possible effect of smoking on SSc presentation and, importantly, SSc progression are lacking. We therefore assessed the association of tobacco exposure with the prevalence and evolution of SSc organ manifestations.

PATIENTS AND METHODS

This study was performed using data from the multinational, longitudinal European Scleroderma Trials and Research (EUSTAR) database (6) (see Appendix A for a list of the EUSTAR coauthors). Each center obtained local ethics committee approval, and each patient provided written informed consent. Data collection started in 2004. The smoking module, however, was introduced to the database in 2013; therefore, smoking data were only collected from that date onward. Data for this study were exported in May 2017.

Patients were included if they were older than age 18 years, fulfilled the 1980 American College of Rheumatology (ACR) or the 2013 ACR/European League Against Rheumatism criteria for SSc (7,8), and if their smoking status was known. Additionally, patients were required to have a follow-up visit 12–24 months after baseline. Information about the core data collected in the EUSTAR database can be found elsewhere (6). The EUSTAR database smoking module collects patient-reported smoking status (never/previous/current smoker), the number of pack-years, and the smoking start and cessation dates.

We assessed the influence of smoking behavior on several disease parameters: forced expiratory volume in 1 second/forced vital capacity ratio (FEV_1/FVC), FVC, single-breath diffusing capacity for monoxide (DLCO), systolic pulmonary arterial pressure (PAP) as estimated by echocardiography, modified Rodnan skin thickness score (MRSS) (9), and DUs. Further information about outcome measures, as well as variables describing the study population, can be found in Supplementary Table 1 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract). Outcome progression was downscaled to "rate of change per 12 months," unless otherwise stated.

Statistical analysis. Frequencies/percentages or means ± SDs were calculated; groups were compared using chi-square test/Fisher's exact test or *t*-test/analysis of variance. Multiple linear and logistic regression analyses were applied to adjust outcome/exposure associations with a priori–defined potential confounding factors (age, sex, time since the onset of Raynaud's phenomenon [RP], time since the first non-RP manifestation, antibody status, and skin involvement). As the SSc-specific antibodies might be on the causal pathway between smoking and SSc organ involvement, we additionally analyzed the data without adjustment for antibody status. These results can be found in Supplementary Tables 2–4 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract).

Three smoking metrics were modeled separately: model 1: never/previous/current smoking; model 2: smoking intensity (pack-years, where never smokers = 0 pack-years, light smokers = 0–10 pack-years, medium smokers = 10–25 pack-years, and heavy smokers = >25 pack-years); and model 3: Comprehensive Smoking Index (CSI). The CSI is an index incorporating smoking duration, time since cessation, and smoking intensity into a single variable (10,11). The CSI depends on 2 parameters that are estimated for each outcome separately: the half-life (i.e., the rate at which the smoking's impact decays over time) and the lag-time (i.e., the delay between smoking and its impact). Never smokers have a CSI score of 0, and higher CSI values indicate more smoking. The CSI values are estimated separately for each outcome variable; therefore, the CSIs, including their ranges, are different for each outcome variable. The results from the CSI regression analyses should be interpreted in the following way: the beta values represent the additive increase or decrease in the outcome variable per unit increase in the CSI. The odds ratio (OR) values represent the increase in odds for the presence of the outcome variable per unit CSI increase. OR values greater than 1 indicate that increased smoking increases the likelihood of occurrence of the outcome.

Missing data were imputed using multiple imputation with chained equations (12). The regression analyses shown in this report are all based on imputed data; the results based on a complete case analysis are represented in Supplementary Table 5 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract). Analyses were performed with Stata/IC15.1.

RESULTS

Patient and smoking characteristics. Of the 12,912 adult SSc patients within the EUSTAR database, 6,179 patients (48%) had no smoking data available, and a total of 3,414 patients (26%) had no follow-up visit in the required time frame. Therefore, 3,319 patients (26%) fulfilled the inclusion criteria (see Supplementary Figure 1, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract). The demographic and disease characteristics of the included and excluded patients were clinically similar (see Supplementary Table 6, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract). Follow-up visits occurred a mean ± SD of 1.4 ± 0.33 years after baseline. The mean age of the patients was 57 years, and 85% were female. Demographic and disease characteristics are shown in Table 1.

A total of 66% of the patients were never smokers, 23% were ex-smokers, and 11% were current smokers; 13% of the current smokers (1.5% of patients) stopped smoking during the observation time, an average of 9 months after the baseline visit. The ex-smokers had smoked a mean ± SD of 18 ± 21 pack-years during a period of 19 ± 12 years and ceased smoking 15 ± 13 years previously. A total of 49% of the ex-smokers had ceased smoking before RP onset, and 58% had quit before the onset of the first non-RP manifestation. The current smokers had smoked a mean ± SD of 27 ± 30 pack-years during a period of 30 ± 13 years.

Table 1. Baseline demographic and disease characteristics of the patients, and outcome measures by smoking status*

Characteristic	No.†	Never smokers (n = 2,205)	Ex-smokers (n = 752)	Current smokers (n = 362)	*P*
Age, years	3,319	57.5 ± 14.1	57.2 ± 12.1	52.5 ± 11.2	<0.001
Male sex, %	3,319	8	27	29	<0.001
Disease characteristics					
Time since RP onset, years	3,286	14.9 ± 11.7	13.4 ± 11.3	13.3 ± 11.8	0.001
Time since first non-RP manifestation, years	2,988	11.7 ± 8.8	10.5 ± 8.7	8.9 ± 7.8	<0.001
Skin involvement, %					<0.001
Sine	3,106	7	8	15	
Limited		64	62	58	
Diffuse		29	30	27	
MRSS	2,949	7.7 ± 7.4	7.8 ± 7.9	6.9 ± 7.3	0.14
Follow-up MRSS	2,839	7.4 ± 7.2	7.2 ± 7.1	6.9 ± 6.9	0.40
Change in MRSS	2,684	−0.3 ± 3.4	−0.6 ± 4.0	−0.2 ± 3.3	0.12
Esophageal symptoms, %	3,275	60	66	58	0.010
Stomach symptoms, %	3,241	23	23	21	0.68
Intestinal symptoms, %	3,250	27	30	29	0.24
Dyspnea NYHA functional class, %		33	34	31	0.001
I	3,114	57	54	63	
II		33	34	31	
III		9	10	5	
IV		1	2	1	
Digital ulcers, current, %	3,125	14	14	16	0.7
Digital ulcers, ever, %	3,125	46	48	45	0.56
% LVEF	2,448	62.3 ± 6.1	61.7 ± 6.3	63.0 ± 5.8	0.015
FEV_1/FVC ratio	2,256	97.5 ± 13.5	95.4 ± 15.2	92.8 ± 15.0	<0.001
Follow-up FEV_1/FVC ratio‡	1,988	97.1 ± 12.0	95.4 ± 14.5	90.5 ± 12.7	<0.001
Change in FEV_1/FVC ratio§	1,656	−0.3 ± 10.1	0.4 ± 9.4	−1.6 ± 7.7	0.065
FVC, % of predicted	2,720	96.1 ± 22.0	96.7 ± 21.3	98.3 ± 19.7	0.25
Follow-up FVC, % of predicted‡	2,435	95.5 ± 22.8	96.3 ± 22.5	99.3 ± 18.8	0.037
Change in FVC, % of predicted§	2,166	−0.6 ± 8.5	−0.4 ± 7.7	0.1 ± 9.4	0.45
Single-breath DLco, % of predicted	2,583	69.8 ± 19.6	66.4 ± 20.4	67.1 ± 17.8	<0.001
Single-breath follow-up DLco, % of predicted‡	2,253	67.5 ± 20.0	65.6 ± 20.0	64.4 ± 18.1	0.021
Single-breath change in DLco, % of predicted§	1,977	−2.0 ± 9.1	−1.7 ± 9.2	−2.0 ± 7.8	0.86
Systolic PAP, mm Hg	2,317	28.8 ± 16.9	26.0 ± 1.0	24.3 ± 12.5	<0.001
Follow-up systolic PAP, mm Hg‡	2,055	29.2 ± 13.6	28.5 ± 14.1	24.7 ± 11.6	<0.001
Change in systolic PAP, mm Hg§	1,706	0.6 ± 10.5	1.6 ± 8.5	0.2 ± 8.1	0.18
Laboratory parameters, %					<0.001
ACA positive	2,508	47	47	61	
Scl-70 positive		45	40	31	
RNAP-III positive		3	6	6	
ESR, mm/hour	2,795	22.8 ± 18.4	18.9 ± 16.7	18.0 ± 14.5	<0.001

* Except where indicated otherwise, values are the mean ± SD. RP = Raynaud's phenomenon; MRSS = modified Rodnan skin thickness score; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; FEV_1/FVC = forced expiratory volume in 1 second/forced vital capacity; DLco = diffusing capacity for carbon monoxide; PAP = pulmonary artery pressure as estimated by echocardiography; ACA = anticentromere antibody; RNAP III = RNA polymerase III; ESR = erythrocyte sedimentation rate.
† Number of patients with available information for each variable.
‡ Based on the follow-up visit, not the 12 months' projection.
§ The changes in outcomes are shown downscaled to "per 12 month."

As patients with interstitial lung disease (ILD) might be more likely to cease smoking than patients without ILD, there might be a higher percentage of ILD patients in the previous smoker group, which could possibly lead to worse trajectories in lung function measures. Therefore, in addition to analyzing the entire study population, we analyzed the progression of lung function measures separately for patients with ILD on high-resolution computed tomography (HRCT) and patients without ILD on HRCT. Among all patients, 49% had signs of ILD on HRCT. The smoking behavior patterns were similar in patients with ILD and in patients without ILD; 68% of patients in both groups were never smokers, 23% of patients with and 20% of patients without ILD were previous smokers, and 9% of patients with and 12% of patients without ILD were current smokers ($P = 0.06$).

FEV_1/FVC ratio. Never smokers had a significantly higher baseline FEV_1/FVC ratio than previous and current smokers (Table 1). These differences in baseline FEV_1/FVC ratio were seen in all 3 smoking models (Figure 1, Table 2, and Supplementary Table 7, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract). As

can be seen in Table 2, patients had a 2.7-unit lower FEV_1/FVC ratio per unit increase in the CSI. Medium and heavy smokers had lower baseline FEV_1/FVC ratios than never smokers and light smokers (all $P < 0.001$) (see Supplementary Table 7, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract). In univariable analysis, the FEV_1/FVC ratio declined similarly across smoking groups ($P = 0.065$); however, in multivariable analysis, the FEV_1/FVC ratio declined faster in current smokers (Figure 1). This result was also observed when stratifying the study population into ILD and non-ILD patients (data not shown).

FVC. There was no significant difference in baseline FVC or in the FVC change between the 3 smoking groups (Table 1). This lack of a robust effect of smoking on the baseline FVC and on the FVC change was also observed in all 3 multivariable models (see Figure 1, Table 2, and Supplementary Table 7, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract). This lack was also observed when assessing the FVC changes separately for ILD and non-ILD patients (data not shown).

Single-breath DLco. Smokers had lower baseline single-breath DLCO levels than never smokers ($P < 0.001$) (Table 1), and smoking was associated with low baseline single-breath DLCO in all 3 models. Single-breath DLCO declined similarly across all 3 smoking behavior groups in univariable analysis (Table 1) and multivariable analysis (see Figure 1, Table 2, and Supplementary Table 7, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract). These results were also seen when ILD and non-ILD patients were assessed separately (data not shown).

Systolic PAP. The average baseline systolic PAP was slightly higher in never smokers than in current or ex-smokers (Table 1). These differences stayed apparent, but to a lesser extent, not only in multivariable assessment of the smoking groups, but also when evaluating smoking intensity and the CSI. The systolic PAP increased similarly in the groups in univariable analysis (Table 1) and multivariable analysis (see Figure 1, Table 2, and Supplementary Table 7, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract).

Skin involvement. Regardless of the smoking matrices used, no association was evident between the severity of skin fibrosis and the smoking history. SSc sine scleroderma, however, was twice as prevalent in current as in ex- or never smokers (Table 1). In all smoking models, no clinically significant difference in MRSS evolution was observed (see Figure 1, Tables 1 and 2, and Supplementary Table 7, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract).

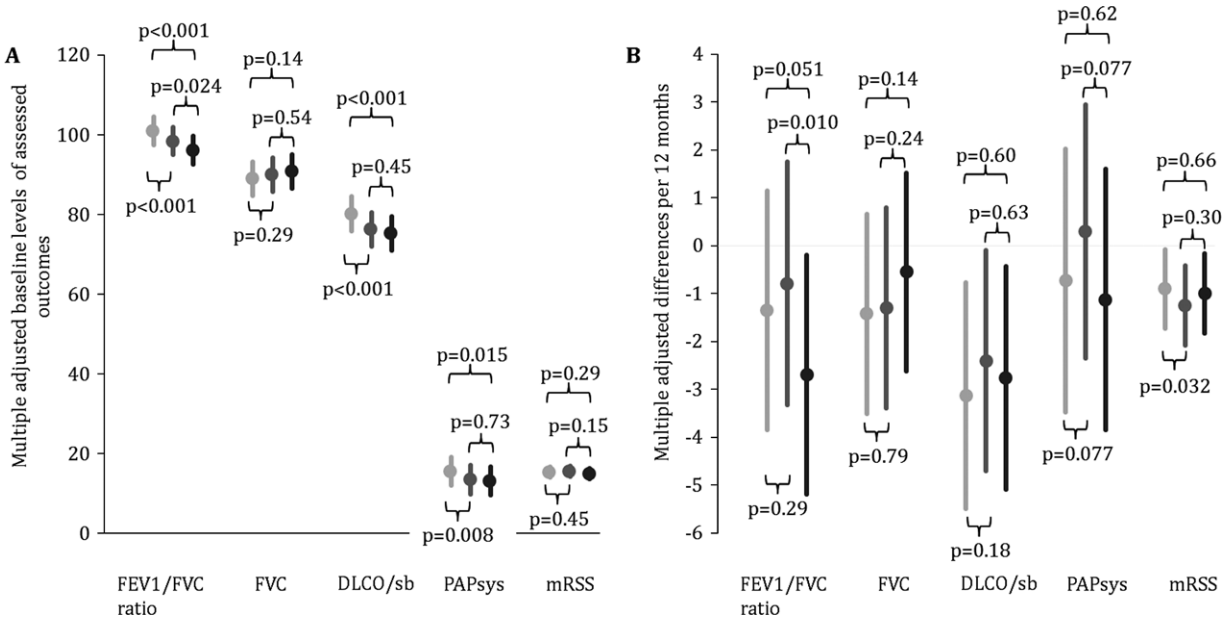

Figure 1. Regression analysis comparing outcomes by smoking status adjusted for age, sex, time since the onset of Raynaud's phenomenon (RP), time since the first non-RP manifestation, antibody status, and extent of skin involvement. **A**, Multiple-adjusted baseline levels of the outcome measures and corresponding 95% confidence intervals (95% CIs). **B**, Multiple-adjusted change rates and corresponding 95% CIs in the outcome measures between baseline and the projected 12-month follow-up. Symbols represent never smokers (light gray), ex-smokers (dark gray), and current smokers (black). FEV_1/FVC = forced expiratory volume in 1 second/forced vital capacity; DLCO/sb = single-breath diffusing capacity for carbon monoxide; PAPsys = systolic pulmonary artery pressure as estimated by echocardiography (mm Hg); MRSS = modified Rodnan skin thickness score.

Table 2. Regression analysis comparing outcomes at baseline and progression of outcomes according to the CSI*

Outcome	CSI, mean (range)†	CSI		
		β‡	95% CI	*P*
Baseline				
FEV_1/FVC ratio	0.45 (0–4.09)	−2.71	−3.46, −1.97	<0.001
FVC	0.34 (0–5.12)	0.41	−0.39, 1.22	0.32
Single-breath DLCO	0.27 (0–2.94)	−4.38	−5.89, −2.88	<0.001
Systolic PAP	0.23 (0–2.61)	−2.08	−3.57, −0.58	0.006
MRSS	0.40 (0–7.05)	0.20	−0.03, 0.43	0.088
DU current	0.35 (0–7.94)	1.19§	1.07, 1.32	0.002
Follow-up¶				
FEV_1/FVC ratio	0.33 (0–6.69)	−0.45	−0.93, 0.02	0.059
FVC	0.46 (0–6.36)	0.32	−0.01, 0.66	0.059
Single-breath DLCO	0.43 (0–4.02)	0.37	−0.16, 0.90	0.17
Systolic PAP	0.35 (0–6.19)	−0.21	−0.76, 0.34	0.45
MRSS	0.43 (0–6.36)	−0.16	−0.29, −0.02	0.021
New DU between visits	0.30 (0–8.37)	0.83§	0.68, 1.00	0.056

* Comprehensive Smoking Index (CSI) scores were adjusted for age, sex, time since the onset of Raynaud's phenomenon (RP), time since the first non-RP manifestation, antibody status, and extent of skin involvement. 95% CI = 95% confidence interval; FEV_1/FVC = forced expiratory volume in 1 second/forced vital capacity; DLCO = diffusing capacity for carbon monoxide; PAP = pulmonary artery pressure as estimated by echocardiography; MRSS = modified Rodnan skin thickness score.
† Illustrates each outcome's CSI score based on the imputed data set. Higher CSI scores indicate more smoking; never smokers have a CSI score of 0.
‡ Beta values represent the additive increase or decrease in the outcome variable per unit increase in the CSI.
§ Value shown is the odds ratio (OR) for current digital ulcer (DU) and new DU between visits in the DU-naive population and represents the increase in odds for the presence of the outcome variable per unit CSI increase. OR values >1 indicate that increased smoking increases the likelihood of occurrence of the outcome.
¶ Assessed the projected change per 12 months of the outcomes.

DUs. The prevalence of DUs was comparable in the smoking behavior groups (Table 1). However, heavy smokers had a greater likelihood of DUs than never smokers in multivariable analysis (OR 1.6, $P = 0.02$) (see Supplementary Table 7, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract). Also, a higher CSI was associated with the presence of DUs at baseline (OR 1.2, $P = 0.002$), i.e., for a 1-unit increase in CSI, the odds of having DUs at baseline increased by a factor of 1.19 (Table 2).

In the subgroup of DU-naive patients at baseline, 14% of never smokers developed new DUs between the 2 visits, compared to 16% ex-smokers and 8% current smokers ($P = 0.05$). Ex-smokers had comparable odds than never smokers to develop DUs between the 2 visits (OR 1.1, $P = 0.7$); current smokers developed DUs less often than never smoking patients (OR 0.5, $P = 0.031$). The smoking intensity was not associated with incident DUs during the observation period (see Supplementary Table 7, available at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract).

DISCUSSION

Our study is by far the largest to prospectively investigate the effect of smoking on SSc outcomes. Smoking was common in our patients; however, it was less common than in Anglo-Saxon cohorts and also much lower than the European average of ~28% (4,5,13).

The EUSTAR cohort replicated the known adverse effect of smoking on bronchial airways in terms of a decline in FEV_1/FVC and DLCO. Given the absence of discernible adverse effects of smoking on systolic PAP, the effect of smoking on diffusion capacity may reflect emphysema rather than precapillary pulmonary vasculopathy. Adverse effects of smoking on pulmonary airway obstruction and diffusing capacity were also seen in 2 cohorts of 137 SSc patients (14) and 19 smokers (15). In accordance with findings in one of these cohorts (14), but in contrast to the second study (15), we found no association between lung compliance (FVC) and smoking status.

This investigation also demonstrated no robust effect of smoking on DU prevalence and incidence when assessing the smoking behavior itself or the smoking intensity, which is similar to the findings in 2 smaller studies (16,17). We even found a negative association between tobacco exposure and incident DUs during the follow-up in a subgroup of DU-naive patients (OR 0.5). This effect could not be explained by differences in immunosuppressive and vasoactive medication (data not shown). However, when we assessed smoking using the CSI, we did find an association of smoking with DU prevalence, which is similar to the results in another, although quite smaller, study also using the CSI (4). This difference could partially arise due to a "healthy smoker effect," although this bias has partly been accounted for by the CSI (18). Given these results, it is difficult to draw robust conclusions on the effect of smoking on DUs.

In our study, smokers had a lower prevalence of Scl-70 autoantibodies than previous and never smokers. This imbalance in autoantibody status is also in accordance with that found in another study, in which Scl-70–positive patients were more likely to be never smokers than ever smokers (2), raising the possibility of an etiopathologic link between smoking and Scl-70 positivity. The question, however, is whether this imbalance is partly due to a link, maybe a causal one, between smoking and autoantibody status, or whether it is partly explained by a "healthy smoker effect," especially as the prevalence of Scl-70 positivity in previous smokers is more comparable to that in never smokers than in current smokers.

Like all registry-based studies, the EUSTAR cohort has limitations. We had no means of verifying the smoking information provided by the patients; however, we were able to demonstrate known adverse

effects of smoking on airway obstruction, suggesting that the information provided by the patients was not random and that our study was powered to detect meaningful changes in other parameters.

By requiring the study population to have a follow-up visit, there is a possibility that we excluded sicker patients, i.e., that we introduced a selection bias for healthier patients. However, at baseline the patients who were excluded due to the absence of a follow-up visit within the required time frame exhibited similar clinical characteristics as the included patients (see Supplementary Table 6, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40557/abstract), which provides evidence against a major selection bias.

In conclusion, our study demonstrates an adverse effect of smoking on pulmonary airways, but no effects on SSc-specific pulmonary and cutaneous involvement. These data provide evidence against a major role of tobacco-associated free radicals and vasoconstrictory and immunomodulatory effects in the pathogenesis of SSc vasculopathy and fibrosis.

ACKNOWLEDGMENTS

EUSTAR acknowledges the unconditional support that the European League Against Rheumatism has provided in the past for the maintenance of the EUSTAR database and the EUSTAR secretariat, as well as the present support of the World Scleroderma Foundation.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Walker had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Jaeger, Distler, Allanore, Walker.

Acquisition of data. Valentini, Hachulla, Cozzi, Distler, Airó, Czirjaák, Allanore, Siegert, Rosato, Matucci-Cerinic, Caimmi, Henes, Carreira, Smith, del Galdo, Denton, Ullman, Langhe, Riccieri, Alegre-Sancho, Rednic, Müller-Ladner, Walker.

Analysis and interpretation of data. Jaeger, Walker.

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