ORIGINAL RESEARCH

Impact of Education on COPD Severity and All-Cause Mortality in Lifetime Never-Smokers and Longtime Ex-Smokers: Results of the COSYCONET Cohort

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Background: Beyond smoking, several risk factors for the development of chronic obstructive pulmonary disease (COPD) have been described, among which socioeconomic status including education is of particular interest. We studied the contribution of education to lung function and symptoms relative to smoking in a group of never-smokers with COPD compared to a group of long-time ex-smokers with COPD.

Methods: We used baseline data of the COSYCONET cohort, including patients of GOLD grades 1–4 who were either never-smokers (n=150, age 68.5y, 53.3% female) or ex-smokers (≥10 packyears) for at least 10 years (n=616, 68.3y, 29.9% female). Socioeconomic status was analyzed using education level and mortality was assessed over a follow-up period of 4.5 years. Analyses were performed using ANOVA and regression models.

Results: Spirometric lung function did not differ between groups, whereas CO diffusing capacity and indicators of lung hyperinflation/air-trapping showed better values in the never-smoker group. In both groups, spirometric lung function depended on the education level, with better values for higher education. Quality of life and 6-MWD were significantly different in never-smokers as well as patients with higher education. Asthma, alpha-1-antitrypsin deficiency, and bronchiectasis were more often reported in never-smokers, and asthma was more often reported in patients with higher education. Higher education was also associated with reduced mortality (hazard ratio 0.46; 95% CI 0.22–0.98).

Conclusion: Overall, in the COSYCONET COPD cohort, differences in functional status between never-smokers and long-time ex-smokers were not large. Compared to that, the dependence on education level was more prominent, with higher education associated with better outcomes, including mortality. These data indicate that non-smoking COPD patients' socioeconomic factors are relevant and should be taken into account by clinicians.

Keywords: COPD, never-smoker, education, socioeconomic status

Introduction

Smoking is considered the major risk factor for COPD. Consequently for the last decades, there has been only minimal scientific interest in COPD in never-smokers. However, data from NHANES III describe, that 6.6% of participants with a spirometric diagnosis of COPD were in fact never-smokers.[1] Other population-based data including the international BOLD survey even demonstrated a never-smoking proportion among COPD of up to 23%.[2,3] Several other risk factors for COPD beyond smoking

have been described. More than 80% of households in China, India and sub-Saharan Africa use biomass for cooking, and in rural areas of Latin America this proportion ranges between 30% and 75%, with a significant impact on death from COPD.[4] In industrialized countries other COPD risk factors like workplace exposures,[2,3] recurrent lower respiratory tract infections, low birth weight, bronchial asthma, history of tuberculosis[5–7] and low socioeconomic status[8] have been identified. As early as 1987, a comparative analysis of Finnish farmers and non-farmers showed that a higher proportion of farmers (2–7%) than non-farmers (0–7%) had COPD, independent of smoking[9] and has been replicated since then.[3] The relative contribution of these factors may differ from country to country, particularly regarding socioeconomic status.[10]

A proper population for comparison might be patients with exposure to a definite risk factor over a sufficient period of time, which has stopped, so that acute, potentially disturbing effects are no more present. This could be ex-smokers for a long time with a certain minimum amount of smoking. Both groups are exposed to socioeconomic risk factors but one of them has an additional exposure known to affect lung function, symptoms and prognosis. By this comparison the contribution from socioeconomic status including education can be analysed, as well as their possible differences to and interactions with cigarette smoking. This type of analysis requires a sufficiently large set of data including both never-smokers and long-time ex-smokers measured under the same conditions. Such data are available in the large and well-characterized COPD cohort COSYCONET (COPD and Systemic Consequences-Comorbidities Network).

Methods
Study Population
The present analysis used the baseline data (visit 1) of the COPD cohort COSYCONET (n = 2741), which is a multi-center study focusing on the role of comorbidities in COPD.[1] Out of 2291 patients with COPD GOLD grades 1–4, 150 patients were identified as never-smokers based on self-reports of smoking behaviour (packyears=0, no active cigarette smoking over lifetime). The group of ex-smokers used for comparison included n=616 patients and was defined as patients who had stopped smoking for at least 10 years and had a smoking history of ≥10 packyears (Figure 1). Further information on the recruitment process and inclusion/exclusion criteria can be found elsewhere.[1] The COSYCONET study has been approved by the ethical committees of all

study centers, and all patients gave their written informed consent.[1] The COSYCONET study was conducted in accordance with the Declaration of Helsinki.

Assessments
Demographic characteristics, socioeconomic variables and the prevalence of comorbidities were assessed based on measurements, questionnaires and standardized interviews. Education was categorized in three groups based on the number of years of education completed (basic education ≤9 years, secondary education 10 to 11 years, higher education >11 years). Household equivalent income was calculated as the net household income per month divided by the number of persons living in the household weighted by age groups.[2] The presence of comorbidities was determined based on patients' reports of physician-based diagnoses, including data on the intake of disease-specific medication.[3] Patients were asked to bring all their medication to the study visit, which was categorized as previously described.[3,4]

Lung function was assessed following the standard operating procedures of COSYCONET, which align with guidelines.[5,6] It included forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and their ratio (FEV_1/FVC), moreover diffusing capacity for carbon monoxide (CO) in terms of transfer factor (TLCO), transfer coefficient (KCO) and alveolar volume (VA). Bodyplethysmographic parameters included intrathoracic gas volume (ITGV), residual volume (RV), total lung capacity (TLC) and the ratio of residual volume to total lung capacity (RV/TLC). For spirometry, we used predicted values provided by the Global Lung Function Initiative (GLI),[6] analogously for TLCO and KCO.[7] Predicted values for body plethysmography were taken from Quanjer et al.[8] Physical capacity was assessed via the Six Minute Walking Distance (6-MWD), timed-up-and-go test (TUG), and the International Physical Activity Questionnaire (IPAQ)[9]. Vascular function was quantified via the ankle-brachial index (ABI).[1,10] Measures of health-related quality of life (HRQL) included the disease-specific COPD Assessment Test (CAT) and the Saint George's Respiratory Questionnaire for COPD patients (SGRQ)[11] with its three components activity, symptoms, and impacts. To capture generic HRQL, we used the Euroqol 5D 3L utility index and the visual analog scale (EQ VAS).[12]

Using the data from follow-up visits, we also examined all-cause mortality over 4.5 years. The survival status was

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assessed by contacting partners, relatives, primary care practitioners and hospitals.[13]

Statistical Analyses

Regarding baseline characteristics of never-smokers and ex-smokers, differences between groups were identified using chi-square tests for categorical variables, and analysis of variance (ANOVA) for continuous variables. To estimate mean values stratified by smoking status and the level of education, we performed multiple ANOVA models. Models were adjusted for age, sex, body mass index (BMI), years since COPD diagnosis and an interaction between smoking status and education. We repeated this analysis excluding all patients with a confirmed physician-based diagnosis of asthma.

The association of comorbidities and medication with smoking status and education was analysed with logistic regression models, while we used proportional hazard Cox regression analysis for mortality. Models were adjusted for age, sex, and BMI and the presence of coronary artery disease. We additionally included $FEV_{1\%}$predicted in the analysis of medication and mortality to account for the severity of the disease.

A sensitivity analysis was performed to determine the robustness of our results while modifying the definition of the group of ex-smokers. For this purpose, three subgroups of ex-smokers were formed based on the number of years since cessation of smoking (10–15 years, 16–25 years, >25 years). Statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC, USA, version 9.4), and p-values of ≤ 0.05 were considered statistically significant.

Results
Study Population

Baseline characteristics of patients are given in Table 1. Within ex-smokers, the mean smoking free interval was 19.3 years (SD ± 9.2). Among non-smokers, the proportion of women was significantly higher; they also showed significantly better lung function in terms of FEV_1/FVC, TLCO, KCO and TLC. In addition, a longer-lasting diagnosis of COPD was found in never-smokers. Regarding physical capacity, never-smokers walked 29 meters more than ex-smokers did in the 6MWD test, while we found no differences in TUG and IPAQ. There were also no significant differences between never- and ex-smokers in terms of educational level, COPD symptoms, PHQ9 and health-related quality of life.

The household net income per months was significantly associated with the level of education and mean income was 1153€ for patients with basic education, 1360€ for secondary education and 1684€ for higher education (Table 2).

Relationship Between Outcome Variables, Smoking Status and Educational Level

Multiple linear regression analysis revealed that educational level was associated with FEV_1, FVC, FEV_1/FVC,
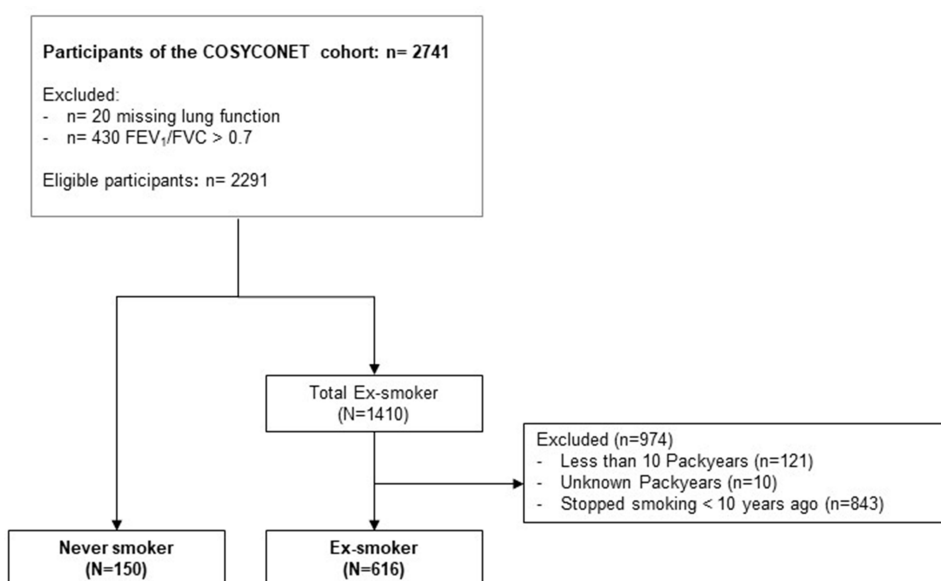

Figure 1 Consort diagram of the study population.

RV/TLC, TLC, 6-MWD, TUG, the total SGRQ and its activity component, as well as EQ-VAS ($p<0.05$ each, Table 3). Smoking status was associated with FEV_1/FVC, ITGV, RV, TLCO, KCO, 6-MWD and the activity component of the SGRQ ($p<0.05$ each, Table 3). The associations between functional parameters, smoking status, HRQL and educational level are illustrated in Figures 2A–D and Figure 3A–C. In general, never-smokers showed better values than ex-smokers, and higher education was associated with better values independent of smoking status. This was reflected in the absence of significant interaction terms between smoking and education (Table 3). When repeating the analysis excluding all patients with the physician-based diagnosis of asthma, we could confirm all results except for FVC and FEV_1/FVC. Here, significant associations with education were no longer present.

Relationship Between Comorbidities, Smoking Status and Educational Level

Table 4 shows the associations between comorbidities, smoking status and educational level found by multiple logistic regression models adjusted for age, sex, and BMI. Never-smokers were more likely to report the diagnoses of asthma, bronchiectasis and alpha-1 antitrypsin deficiency (AATD, $p<0.05$ each). We found no associations between comorbidities and educational level, except for asthma, which was associated with the highest level, and for AATD, which was associated with secondary education.

Relationship Between Medication, Smoking Status and Educational Level

When using multiple logistic regression analyses adjusted for age, sex, BMI and FEV_1%predicted, we found no significant associations between the prescription of medication and smoking status as well as educational level (see Table S1).

Relationship Between Mortality, Smoking Status and Educational Level

Higher education was associated with a reduced mortality over the follow-up time of 4.5 years (HR 0.46 95%-CI [0.22–0.98], see Table S2). This was accompanied by associations with age (HR 2.77 95%-CI [1.94–3.95] for 10 years increase of age) and FEV_1%predicted (HR for a decrease of 10% 1.29 95%-CI [1.12–1.49]). Regarding smoking status, there was only a tendency towards an association with reduced mortality in never-smokers (HR

0.84 95%-CI [0.45–1.60]). Coronary artery disease was not a significant predictor for mortality.

Sensitivity Analyses

When repeating the analyses stratified according to the duration of ex-smoking (group 1: 10–15 years, n=294; group 2: 16–25 years, n=187; group 3: ≥26 years, n=135) we confirmed the results for education in all three sub-groups. Regarding the effects of smoking, differences between never-smokers and ex-smokers were maintained in groups 1 and 2, whereas no differences were detected in group 3, ie, patients with the longest time of ex-smoking (see Table S3).

Exclusion of Patients with the Physician-Based Diagnosis of Asthma

We repeated all analyses excluding the patients with the additional physician-based diagnosis of asthma. All results and the respective tables are provided in Tables S4-S7 and confirmed the previous results. Only the examination of mortality showed that the beneficial effect of higher education was no longer significant (p= 0.1438), however, the direction of the estimate (HR = 0.52) remained unchanged and indicate a lower mortality in the high education group. Due to the now lower number of cases, only n=58 cases could be included in the mortality analysis.

Discussion

In the present study, we compared never-smokers with COPD with long-time ex-smokers with COPD in order to reveal whether, in the absence of the acute challenge of active smoking, these two groups showed different characteristics. Overall, never-smokers showed better functional and clinical characteristics, but the major determinant of differences in both groups was the level of education. In addition to age and lung function, educational level was a major predictor of mortality, in contrast to smoking history. These data suggest benefits on functional and clinical status as well as mortality linked to higher education, which even dominated smoking, if the time of ex-smoking was long.

Spirometric lung function did not differ between never-smokers and ex-smokers, whereas CO diffusing capacity and indicators of lung hyperinflation/air-trapping showed better values in the never-smokers. In both groups, spirometric lung function but not the other markers depended on education level, with better values for higher education. Since adult and childhood socioeconomic status (SES) are correlated,[14] it can be assumed that a low socioeconomic status was also present in childhood. Low family SES and low educational level of

Table 1 Baseline Characteristics of the Study Sample Stratified by Smoking Status

n		Never-Smoker	Ex-Smoker	p-value[a]
		150	**616**	
Male		70 (46.7)	432 (70.1)	<0.0001
Age, yrs		68.5 ± 8.4	68.3 ± 7.7	0.7268
BMI category[b]	Underweight	4 (2.7)	10 (1.6)	0.0531
	Normal	65 (43.6)	201 (32.7)	
	Overweight	54 (36.2)	265 (43.1)	
	Obese	26 (17.5)	139 (22.6)	
Education[c]	Basic education	77 (51.3)	349 (56.7)	0.4924
	Secondary education	41 (27.3)	153 (24.8)	
	Higher education	32 (21.3)	114 (18.5)	
Pulmonary function	FEV_1% pred	55.2 ± 18.4	53.1 ± 19.1	0.2337
	FVC % pred	76.8 ± 19.7	78.8 ± 19.3	0.2632
	FEV1/FVC (L)	54.9 ± 10.2	51.1 ± 11.1	**0.0001**
	TLCO % pred	65.2 ± 25.4	57.4 ± 22.5	**0.0003**
	KCO % pred	79.5 ± 29.0	67.1 ± 22.6	**<0.0001**
	ITGV % pred	140.8 ± 31.9	146.0 ± 37.6	0.1208
	RV % pred	160.1 ± 45.4	167.2 ± 53.0	0.1423
	RV/TLC	0.55 ± 0.10	0.55 ± 0.11	0.6735
	VA % pred	82.8 ± 16.8	84.4 ± 15.2	0.2719
	TLC % pred	123.5 ± 35.0	115.9 ± 31.2	**0.0095**
GOLD group (mMRC)	A	60 (41.1)	232 (37.9)	0.8571
	B	36 (24.7)	169 (27.6)	
	C	20 (13.7)	80 (13.1)	
	D	30 (20.6)	131 (21.4)	
Severe exacerbation history	Proportion Yes	24 (16.0)	116 (18.9)	0.4164
	Mean annual rate	1.6 ± 0.7	1.4 ± 0.8	0.3806
Years since COPD diagnosis		12.3 ± 9.8	10.7 ± 7.6	0.0278
AATD		34 (22.7)	60 (9.7)	**<0.0001**
Symptoms and Quality of life	mMRC	1.5 ± 0.9	1.6 ± 0.9	0.1974
	SGRQ	42.1 ± 18.9	43.8 ± 19.9	0.3238
	activity	55.8 ± 24.5	60.3 ± 25.7	0.0555
	symptoms	54.6 ± 21.9	54.4 ± 21.1	0.9192
	impacts	29.5 ± 20.1	30.5 ± 20.6	0.6065
	CAT	17.5 ± 7.2	18.0 ± 7.2	0.4900
	EQ-VAS	56.7 ± 19.3	55.8 ± 19.6	0.6219
	EQ-5D utility	0.83 ± 0.19	0.82 ± 0.19	0.5629
PHQ-9		5.66 ± 3.99	5.81 ± 4.36	0.7002
TUG		6.76 ± 2.01	7.13 ± 2.59	0.1034
IPAQ		4270.8 ± 4177.8	4373.9 ± 5947.0	0.8441
6MWD		434.3 ± 109.2	405.3 ± 108.5	**0.0038**
ABI		1.25 ± 0.12	1.19 ± 0.14	**<0.0001**

Notes: Data are presented as n (%) or mean ± standard deviation. [a] p-value based on Chi^2-test (categorical variables) and based on ANOVA (continuous variables). [b] Normal weight (18.5 ≤ BMI <25), overweight (25 ≤ BMI < 30), obese (BMI ≥ 30), and underweight (BMI < 18.5). [c] Basic education (≤9 school years), secondary education (10–11 school years), and higher education (>11 school years). Significant differences between groups are marked in bold (p<0.05).

Table 2 Mean Household Net Income per Month in Euro by Level of Education

	Mean ± SD	p-value[a]
Basic education (≤9 years)	1153 ± 561	<0.0001
Secondary education (10–11 years)	1360 ± 560	
Higher education (>11 years)	1684 ± 674	

Note: [a] p-value based on ANOVA.

parents have been described as being associated with a higher risk of chronic infections,[15] which in turn would favour a long-term deterioration of lung function. Furthermore, it can be expected that low socioeconomic status is associated with further lifestyle factors that have a negative effect on lung function, such as air pollution, unhealthy diet, passive smoking and indoor climate.[16–18] Thus, negative effects on lung function as observed in our study are consistent with previous findings. Our findings are also in accordance with previous investigations showing faster FEV_1 decline at least in less-educated females, independent of smoking.[19] As potential mechanistic factors, associations between low SES and elevated systemic inflammatory burden have been proposed.[20]

Smoking is known to induce multiple changes in the lung, including alterations in small airways and alveolar structure,[21] which are reflected in measures of peripheral airway function, in particular hyperinflation/air-trapping and gas exchange capacity. In accordance with this, we found smoking linked to these parameters. It might therefore be speculated, that the peculiar pattern of lung

Table 3 Mean Values of Parameters by Smoking Status and Education

	Basic Education (≤9 Years)		Secondary Education (10–11 Years)		Higher Education (>11 Years)		Main Effects		Interaction
	Never-Smoker	Ex-Smoker	Never-Smoker	Ex-Smoker	Never-Smoker	Ex-Smoker	Education	Smoking	Education* Smoking
n	77	349	41	153	32	114	p-value		
Lung function parameters									
FEV_1% pred	49.3	48.7	52.3	51.2	61.3	53.0	**0.0012**	0.0754	0.1958
FVC % pred	70.7	74.3	74.8	77.6	80.0	78.1	**0.0118**	0.4347	0.4773
FEV1/FVC (L)	52.9	49.6	53.4	49.9	57.8	51.3	**0.0275**	**<0.0001**	0.4313
TLCO % pred	62.6	51.7	62.3	53.4	64.6	56.9	0.4229	**<0.0001**	0.8178
KCO % pred	79.5	62.4	77.7	65.2	77.6	69.0	0.7838	**<0.0001**	0.3492
RV/TLC	0.58	0.58	0.57	0.56	0.53	0.56	**0.0096**	0.3502	0.4299
ITGV % pred	150.8	156.4	144.9	159.2	140.0	152.6	0.2110	**0.0021**	0.4552
RV % pred	173.3	178.9	165.7	181.4	156.8	172.5	0.1540	**0.0140**	0.5465
VA % pred	84.8	82.9	77.7	83.7	82.7	81.3	0.1838	0.5704	0.0633
TLC % pred	122.5	123.2	125.2	123.5	113.5	118.4	**0.0490**	0.6394	0.6554
Symptoms, health-related quality of life, exercise capacity and functioning									
SGRQ	44.5	47.3	43.0	43.2	37.8	39.5	**0.0081**	0.4270	0.8275
Activity	60.0	65.5	58.8	60.8	44.7	55.6	**0.0001**	**0.0146**	0.4076
Symptoms	55.4	55.3	51.9	54.6	55.8	49.7	0.4939	0.5973	0.3025
Impacts	31.5	33.8	30.3	29.0	27.5	26.4	0.0571	0.9968	0.6647
CAT	18.7	19.4	18.0	17.9	16.4	17.6	0.0518	0.4059	0.7418
EQ-VAS	53.9	51.4	56.1	54.0	57.7	59.3	**0.0422**	0.6068	0.6610
EQ-5D utility	0.78	0.79	0.86	0.78	0.81	0.84	0.1229	0.3552	0.1140
mMRC	1.59	1.76	1.65	1.67	1.42	1.50	0.1329	0.3290	0.7365
IPAQ	3591.4	3844.7	4111.0	3500.6	3786.3	3857.7	0.9847	0.8698	0.7898
6MWD	424.9	390.0	416.9	403.3	484.7	426.2	**0.0004**	**0.0007**	0.2757
Time up and go	6.86	7.21	6.55	6.97	5.99	6.60	**0.0422**	0.0615	0.9139
PHQ9	6.11	6.96	6.29	6.36	6.79	6.46	0.8553	0.6406	0.4436
ABI	1.26	1.18	1.23	1.20	1.27	1.19	0.8192	**<0.0001**	0.2178

Notes: Models were adjusted for age, sex, BMI, and time since COPD diagnosis. *marks the interaction between school and smoking. Significant associations are marked in bold (p<0.05).
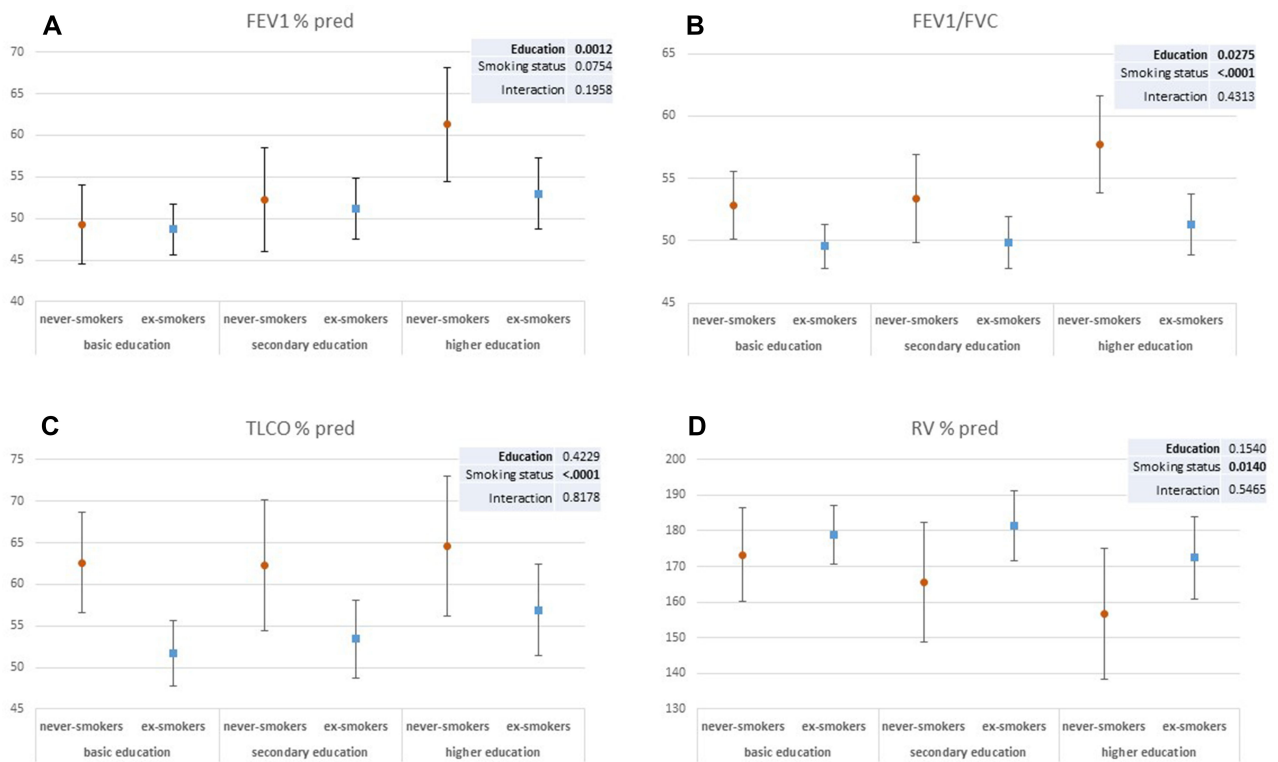
Figure 2 Mean values of lung function parameters by smoking status and by education. Multiple ANOVA models (**A–D**) were adjusted for age, sex, body mass index (BMI), years since COPD diagnosis, and smoking status*education. Education was categorized as basic education (≤9 years), secondary education (10–11 years), and higher education (>11 years).

function alteration that we observed reflects differential effects of smoking and socioeconomic history or status as reflected in educational level. In our study population, occupation was part of the socioeconomic status linked to education.

The positive influence of educational level was also reflected in better health-related quality of life and physical capacity, which was true in both never-smokers and ex-smokers. Probably, both lung function and life-style factors played a role, in accordance with previous results,[22] as well as data showing that psychosocial exposures can influence long-term health through mechanisms such as learned behaviour.[14] For example, the probability of being a smoker or drinker decreases very strongly with higher SES, an accepted proxy for education,[14,23,24] while at the same time the consumption of healthy diet and the desire for regular physical activity increases. Other studies even found a direct link between lower educational level and decreased physical activity, based on both, material problems and poor perceived health experience.[25]

The association of asthma with educational level has multiple aspects. A low educational level might favour childhood risk factors of asthma,[26] but a high level also,

for example, via the hygiene hypothesis.[27] The association of asthma with never-smoking could be the result of medical recommendations or early experiences. Moreover, in patients without a history of smoking, physicians may be more inclined to consider asthma, but also bronchiectasis and A1AT deficiency as comorbidity. By contrast, it could be assumed that never-smoker patients are not genuine COPD but asthma patients. To elucidate this, we conducted a sensitivity analysis by excluding patients with the medical record of concomitant asthma. The significant association of education with FEV_1 remained essentially unchanged.

We observed no associations of respiratory treatment with the level of education or smoking history, probably as result of unrestricted access to health-care providers and adequate pulmonary treatment. An earlier study in COSYCONET patients showed that the overall treatment adherence was very high, suggesting that the differences found in our study were not due to differences in treatment adherence.[28] Furthermore, a recent publication in COSYCONET[22] showed no significant relationship between education and the use of non-pharmacological interventions in COPD including COPD sport programmes and patient
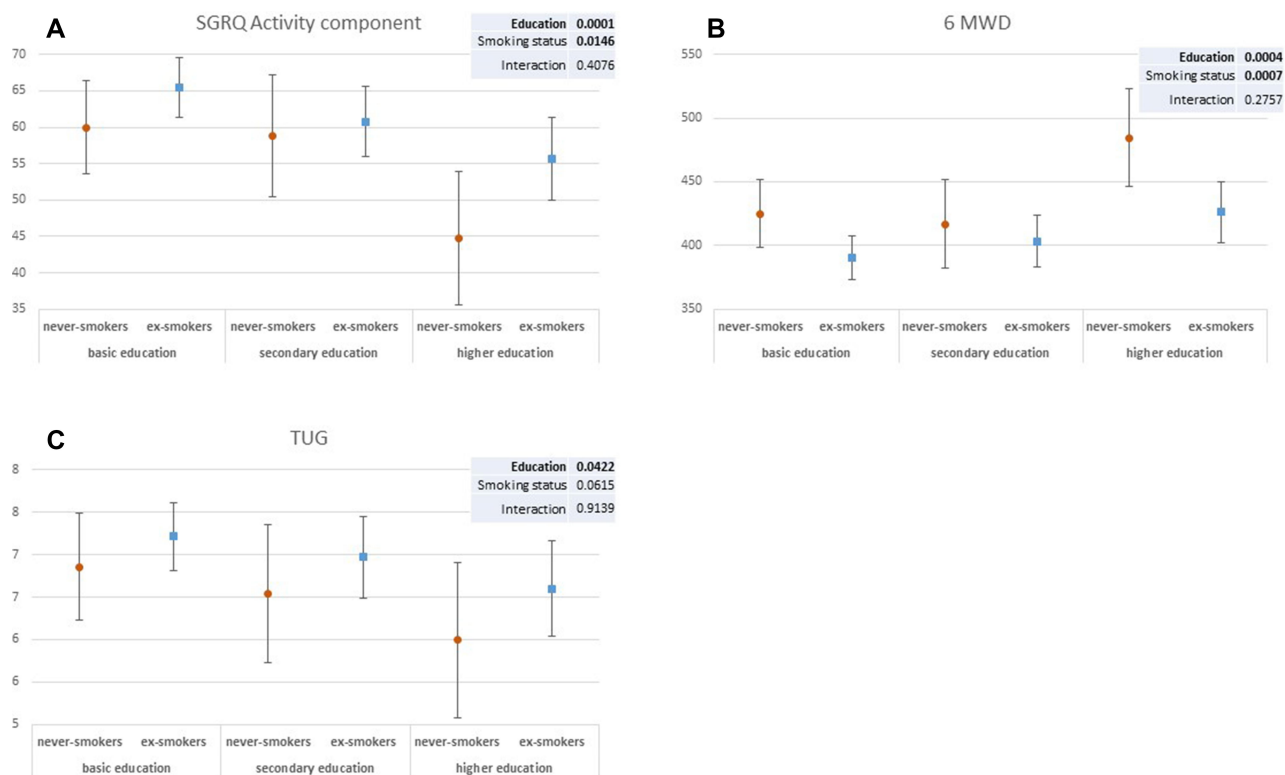
Figure 3 Mean values of health-related quality of life and exercise capacity by smoking status and by education. Multiple ANOVA models (**A–C**) were adjusted for age, sex, body mass index (BMI), years since COPD diagnosis, and smoking status*education. Education was categorized as basic education (≤9 years), secondary education (10–11 years), and higher education (>11 years).

training. We therefore assume that the association between higher education and better lung function is not based on differences in treatment or access to public health care, at least in the cohort studied, which certainly represents a positive selection. Accordingly, it can be concluded that the effect of education on health status can be attributed to the combined risk factors in life history rather than to major differences in the actual treatment of COPD. We included only patients who did not have any burden from cigarette smoke either for a long time or ever. The residual effects from smoking could still be recognized in terms of reductions in gas uptake capacity, which involves changes in both

Table 4 Association Between Comorbidities, Smoking Status, and Education

	Education			Smoking Status	
	Basic (≤9 Years)	**Secondary (10–11 Years)**	**Higher (>11 Years)**	**Ex-Smoker**	**Never-Smoker**
		OR (95% CI)	*OR (95% CI)*		*OR (95% CI)*
AATD	ref.	**2.01 (1.16–3.47)**	1.54 (0.84–2.84)	ref.	**2.60 (1.55–4.37)**
Diabetes	ref.	0.81 (0.47–1.38)	0.69 (0.38–1.24)	ref.	1.02 (0.57–1.81)
Hypertension	ref.	1.26 (0.87–1.83)	1.08 (0.72–1.61)	ref.	0.89 (0.61–1.31)
Asthma	ref.	1.06 (0.69–1.63)	**1.99 (1.28–3.08)**	ref.	**2.34 (1.57–3.49)**
KHK	ref.	0.76 (0.47–1.23)	0.72 (0.43–1.20)	ref.	0.75 (0.43–1.30)
Bronchiectasis	ref.	0.85 (0.37–1.96)	1.22 (0.54–2.74)	ref.	**5.00 (2.55–9.81)**
Hyperuricemia	ref.	0.88 (0.56–1.40)	0.76 (0.46–1.26)	ref.	0.89 (0.53–1.48)
HLP	ref.	0.92 (0.65–1.31)	0.75 (0.51–1.10)	ref.	0.91 (0.63–1.32)
Osteoporosis	ref.	0.69 (0.43–1.09)	0.63 (0.37–1.08)	ref.	1.48 (0.95–2.31)
GI	ref.	0.83 (0.59–1.18)	0.74 (0.50–1.08)	ref.	0.78 (0.54–1.13)

Notes: Logistic regression models were adjusted for age, sex, and BMI (estimates not shown). Significant associations are marked in bold (p<0.05).

ventilation and pulmonary capillary perfusion. In accordance with this, the ankle-brachial index was slightly reduced in ex-smokers but not dependent on educational level. As there were no significant differences in cardiovascular comorbidities between never- and ex-smokers, this suggests a differential effect of smoking on cardiovascular status. It could be that the diagnosis of a comorbidity is more difficult in the presence of COPD.[29] The absence of differences in the prevalence of cardiovascular comorbidities was consistent with the finding that cardiovascular disease was not involved in the prediction of mortality, in contrast to educational level that was predictive even when accounting for FEV_1%predicted, age, BMI and sex. These observations underlined the major importance of educational level.

Limitations

Information indicating a previous diagnosis of tuberculosis, which could also be a risk factor for COPD, was given by n=21 patients; due to the small sample size, we did not address this topic in our analyses. A number of factors experienced during childhood are known to influence the development of respiratory diseases, but also lung function in adulthood. These include low birth weight, premature birth, repeated respiratory infections in childhood, and prenatal and later exposure to passive smoking.[30] Such data was not collected in COSYCONET, so that a further evaluation was not possible. SES trajectories, such as downward or upward social mobility, may increase and decrease risk of cardiovascular disease.[31] In COSYCONET only the last SES was surveyed, but the educational level as achieved at an early age in most cases, could be regarded as long-term indicator of SES, in particular with regard to life-style factors. Lower SES is also associated with poorer living conditions such as increased air pollution. However, a corresponding assessment could not be made as due to data safety restrictions only a three-digit postal code was provided by the patients which does allow for a precise determination of their living conditions, eg, proximity to major roads and a present place of residence does not reveal the respective past living conditions.

Conclusion

In never-smokers with COPD and ex-smokers since at least 10 years, the educational level, as indicator of socioeconomic status, had an impact on clinical and functional status as well as mortality. In the ex-smokers, residual effects of smoking in terms of air-trapping and gas exchange were still present. It is a reasonable expectation that among COPD patients the proportion of non-smokers, including long-time ex-

smokers, will increase. Our findings suggest that in these patients, assessments should include socioeconomic status/ education as cumulative indicator of risk factors in life history independent of smoking. The risk group of low educational status may need special care in disease-management programmes for a more regular monitoring of health status and, if necessary, earlier intervention.

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Names of Participating Study Nurses

Data Sharing Statement

Ethics Approval and Consent to Participate

Consent for Publication

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed on the journal to which the article will be submitted; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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