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Cumulative occupational exposure to gases and fumes is associated with impairment in lung function and disease-related quality of life in a German COPD patient cohort

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ABSTRACT

Objectives The impact of occupational exposures on lung function impairments and quality of life (QoL) in patients with chronic obstructive pulmonary disease (COPD) was analysed and compared with that of smoking.

Methods Data from 1283 men and 759 women (Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades 1–4 or former grade 0, without alpha-1-antitrypsin deficiency) of the COPD and Systemic Consequences Comorbidities Network cohort were analysed. Cumulative exposure to gases/fumes, biological dust, mineral dust or the combination vapours/gases/dusts/fumes was assessed using the ALOHA job exposure matrix. The effect of both occupational and smoking exposure on lung function and disease-specific QoL (St George's Respiratory Questionnaire) was analysed using linear regression analysis adjusting for age, body mass index, diabetes, hypertension and coronary artery disease, stratified by sex.

Results In men, exposure to gases/fumes showed the strongest effects among occupational exposures, being significantly associated with all lung function parameters and QoL; the effects were partially stronger than of smoking. Smoking had a larger effect than occupational exposure on lung diffusing capacity (transfer factor for carbon monoxide) but not on air trapping (residual volume/total lung capacity). In women, occupational exposures were not significantly associated with QoL or lung function, while the relationships between lung function parameters and smoking were comparable to men.

Conclusions In patients with COPD, cumulative occupational exposure, particularly to gases/fumes, showed effects on airway obstruction, air trapping, gas uptake capacity and disease-related QoL, some of which were larger than those of smoking. These findings suggest that lung air trapping and QoL should be considered as outcomes of occupational exposure to gases and fumes in patients with COPD.

Trial registration number NCT01245933.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Occupational exposures are a risk factor for chronic obstructive pulmonary disease (COPD), and patients with COPD often report relevant occupational exposures.

WHAT THIS STUDY ADDS

⇒ Occupational exposures, especially those to gases and fumes, were associated with airway obstruction, air trapping, reduced gas uptake capacity and impaired health-related quality of life in patients with COPD; and partially even more so than smoking history in terms of pack years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Reduced quality of life and air trapping/lung hyperinflation should be considered as indicators of occupational exposure effects in patients with COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by a not fully reversible and usually progressive airflow obstruction. Moreover, COPD is frequently accompanied by comorbidities. With an estimated global prevalence of approximately 12% (15% in men and 10% in women),[1] COPD is currently the third leading cause of death worldwide.[2] Although the majority of COPD cases in the developed world are attributable to cigarette smoking, it occurs also in non-smokers, among whom occupational risk factors significantly contribute to the development of COPD.[3] Occupational exposures to vapours, gases, dusts and fumes (VGDF) have been linked to the development of COPD[4] and were reported to account for a median value of 10–15% of COPD risk,[3 5] after controlling for smoking.[5]

Occupational exposures to VGDF often occur together with exposure to cigarette smoke, and disentangling these effects is challenging. Common

COPD comorbidities[6] might also play a role, as data have shown associations between ambient air pollution and the development of diabetes,[7] hypertension[8] and coronary artery disease.[9] Thus, these comorbidities might arise partially through inhaled compounds, potentially including occupational exposures. In addition, systemic inflammation in COPD might play a role,[10] as well as the associations between comorbidities and lung function.[11] This suggests taking into account smoking history and comorbidities when analysing effects of airborne occupational exposures on the lung. Such exposures can be estimated based on patients' occupational history using the well-established ALOHA job exposure matrix (JEM).[12–15] This matrix appeared particularly well suited for the data available in the present study. As occupational exposures might have multiple effects on airway obstruction, lung hyperinflation, gas exchange capacity, health-related quality of life and comorbidities in patients with COPD, a comprehensive analysis of their effects might be helpful to better understand both, exposures and COPD, but such an analysis is not available.

We thus investigated the impact of occupational exposure to biological dusts, mineral dusts, gases and fumes, and the composite measure VGDF on multiple measures of COPD status in patients from the COPD and Systemic Consequences Comorbidities Network (COSYCONET)[16] cohort and compared this with the effects of smoking.

METHODS

We used data on job history, lung function, comorbidities, anthropometric measures and demographics from the COSYCONET recruitment visit.[16] This cohort comprises 2741 patients with COPD investigated in comprehensive assessments in 31 study centres throughout Germany; the study protocol and the inclusion and exclusion criteria were described previously.[16] Written informed consent was obtained from all participants.

Exposure assessment

Patients' occupational history was assessed by free text self-reports on their last four jobs and corresponding employment durations. Reported occupations were coded according to International Standard Classification of Occupations 2008 (ISCO-08)[17] by two researchers independently. Jobs coded differently or not listed in the ISCO-08 scheme were re-evaluated by an occupational medicine expert. The ISCO-08 codes were made compatible with the ISCO-88 coding required by the ALOHA JEM via ISCO correspondence tables.[18] By combining the ISCO-88 codes with the ALOHA JEM, exposure to biological dusts, mineral dusts, gases and fumes, or the composite measure VGDF could be estimated.[12–15] For each job, exposure was assessed as no exposure=0, low exposure=1 or high exposure=2 for each of the four agents. Each patient's cumulative occupational exposure for all reported jobs was calculated by summarising the products of the number of employment years and the corresponding squared exposure levels for each reported job. Patients' cigarette smoke exposure was quantified in terms of pack years.

Outcome assessment

Lung function measurements followed standardised protocols and were based on postbronchodilator data and internationally accepted quality criteria.[16] For this analysis, we used:

- Data on forced expiratory volume in 1 s (FEV_1) as indicator for airway obstruction in COPD.
- The per cent ratio of residual volume to total lung capacity (RV/TLC %) as determined in body plethysmography measurements as indicator for air trapping.
- The transfer factor for carbon monoxide (TL_{CO}) from single-breath measurements as indicator for gas exchange capacity.

Values of FEV_1 and TL_{CO} were expressed as per cent of predicted values based on age, height, sex and ethnicity.[19 20] RV/TLC % values were used directly, as age and body mass index (BMI) were carried as covariates in the analyses. FEV_1 %predicted and the ratio FEV_1/forced vital capacity (FVC) were used to categorise patients with $FEV_1/FVC<0.7$ into Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades 1–4.[21] COSYCONET also includes patients with $FEV_1/FVC\geq0.7$ and symptoms of chronic bronchitis, which were formerly regarded as patients 'at risk' (GOLD category 0).[22] They were kept in the analyses since they had comorbidities and symptoms similar to those of GOLD grades 1–4 and their inclusion increased the range of variation in lung function measures. On the other hand, individuals with $FEV_1/FVC\geq0.7$ without symptoms of chronic bronchitis at the time of the study (n=90) were excluded from the analysis. Patients with physician-based diagnosis of alpha-1-antitrypsin deficiency (n=125) were also excluded since they may show a different sensitivity to airborne exposures than patients without this deficiency. The process by which the final study population was defined is illustrated in online supplemental figure S2.

Using a well-established tool, health-related quality of life was assessed using the total score of the St George's Respiratory Questionnaire.[16 23 24] Scores range from 0 to 100 with higher scores indicating larger degrees of impairment.

Comorbidities

The presence of comorbidities was assessed in structured interviews.[16] A comorbidity was assumed present if the patient reported physician-diagnosed disease or, in the absence of such a report, if disease-specific medication was identified.[25] We included the three major COPD comorbidities hypertension, diabetes and coronary artery disease in the analysis.

Statistical analysis

For description, median values and quartiles, and frequencies and percentages are presented. Due to skewness of distributions, exposure levels were compared between patients with and without comorbidities and between men and women using Mann-Whitney U test, and correlation between exposures was quantified by Spearman rank correlation. Due to significant correlations between the exposure measures, linear regression analyses with lung function parameters as dependent variables were performed separately for each of the four exposure measures. These analyses were stratified for sex and adjusted for age, BMI, pack years and the three comorbidities as the major factors that are known to have an effect on lung function. In order to quantify the potential effects of exposures as detailed as possible, we focused on the single occupational exposure measures instead of the composite exposure VGDF. The single exposures showing the strongest reliable associations with lung function parameters were included in the final regression models. To visualise the effects of occupational exposure and smoking, we multiplied the observed IQRs of occupational exposures and pack years with the respective regression coefficients from the final linear regression analysis. This quantified their contributions to the impairments in lung function parameters and quality

Table 1 Baseline characteristics (median with first and third quartiles/frequencies) of the total study population with complete cases and stratified by sex

	Total (N=2042)	Men (n=1283)	Women (n=759)	% missing (of N=2741)
	Median (Q1, Q3)	Median (Q1, Q3)	Median (Q1, Q3)	n (%)
Confounders				
Age (years)	65.0 (59.0; 71.0)	67.0 (60.0; 72.0)	63 (58.0; 69.0)	0 (0)
BMI (kg/m^2)	26.6 (23.7; 30.1)	27.1 (24.3; 30.4)	25.5 (22.2; 29.6)	2 (0.1)
Pack years	43.0 (23.0; 66.3)	47.0 (26.0; 74.0)	38 (20.0; 57.0)	234 (8.5)
Outcomes				
FEV_1 %predicted	55.0 (41.3; 70.6)	54.2 (40.4; 69.6)	56.5 (42.1; 72.4)	16 (0.6)
RV/TLC %	52.8 (45.6; 60.8)	51.2 (44.2; 59.2)	54.8 (47.6; 62.8)	102 (3.7)
TL_{CO} %predicted	56.8 (42.5; 73.2)	57.6 (43.2; 73.9)	55.59 (40.0; 72.0)	246 (9.0)
SGRQ (score)	40.6 (27.9; 56.5)	40.2 (27.6; 56.2)	41.5 (28.2; 57.4)	27 (1.0)
Comorbidities				
Diabetes, n (%)	294 (14.4)	236 (18.4)	58 (7.6)	0 (0)
Coronary artery disease, n (%)	362 (17.7)	296 (23.1)	66 (8.7)	88 (3.2)
Hypertension, n (%)	1185 (58.0)	791 (61.7)	394 (51.9)	88 (3.2)

Patients were of Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades 1–4 and of former grade 0 without alpha-1-antitrypsin deficiency.
BMI, body mass index; FEV_1 %predicted, percentage of predicted value of forced expiratory volume in 1 s; Q1, first quartile; Q3, third quartile; RV/TLC %, per cent ratio of residual volume to total lung capacity; SGRQ, St George's Respiratory Questionnaire; TL_{CO} %predicted, percentage of predicted value of transfer factor for carbon monoxide from single-breath measurements.

of life for typical ranges of exposures in the study cohort. To better understand the pattern of direct and indirect relationships between variables and compare it between men and women, structural equation modelling (SEM) was employed (see online supplemental material). The data set used for all of these analyses was required to have complete data in all parameters.

Statistical significance was assumed for $p<0.05$, parameter estimates are presented as point estimates with 95% CIs. All analyses were performed using SPSS software (V.26).

RESULTS

Descriptive analysis

The population of participants with complete variables of interest comprised 2042 patients (1283 men, 759 women), of whom 167/790/692/144 were categorised as GOLD grades 1/2/3/4, respectively, and 249 as former GOLD grade 0 (online supplemental figure S2). Baseline characteristics and prevalence of comorbidities are presented in table 1. Prevalence of exposure and cumulative occupational exposure levels are shown in online supplemental table S1, stratified by sex. Compared with men, the overall occupational exposure in women was significantly lower, except for biological dust. While the highest prevalence was observed for gases and fumes exposure in both men and women, mineral dust exposure was least prevalent in women and biological dust exposure was least prevalent in men. In men, cumulative exposure to biological dust was the lowest, while cumulative exposure to gases and fumes was the highest reported. In women, cumulative exposure to mineral dust was very low, while the highest cumulative single exposure was that to gases and fumes.

Prevalence and associations between COPD symptoms and comorbidities differed between men and women, as previously reported.[26] Thus, subsequent analyses were stratified by sex.

Occupational exposures and lung function measures

Occupational exposure measures were statistically significantly correlated with each other, particularly exposure to gases and fumes with combined exposure to VGDF (online supplemental table S2). There were also correlations between exposure to mineral dust, exposure to biological dust, combined exposure to VGDF and pack years in men. The correlations of the occupational exposures and smoking were much weaker than between different occupational exposures. No statistically significant associations were found between the four exposure measures and comorbidities (online supplemental table S3). As commonly found in patients with COPD, there were statistically significant correlations between comorbidities and FEV_1 %predicted, RV/TLC % and TL_{CO} %predicted. To account for this, comorbidities were carried as covariates in the following regression analyses, despite their lack of association with occupational exposures (Mann-Whitney U test, online supplemental table S3).

Table 2 presents standardised regression coefficients corresponding to the unadjusted associations of the occupational exposure measures with the lung function parameters and the quality of life score, controlling for age, BMI, pack years and comorbidities. In men, nearly all exposures and dependent variables were significantly associated with each other, with the strongest associations for exposure to gases and fumes and quality of life. In women, exposure to mineral dust was significantly associated with quality of life and RV/TLC %, while exposure to gases and fumes was associated with quality of life only. However, exposure to mineral dust in women was overall rather infrequent and low, with some heavy outliers, thus the observed associations were not deemed reliable. To enhance comparability with men, exposure to gases and fumes was chosen for the final multivariate regression models in women as well.

Results of regression models adjusted for smoking, comorbidities and confounders are presented in table 3. In men, exposure to gases and fumes was significantly linked to all four outcomes. Pack years were associated with TL_{CO} %predicted only. In women, exposure to gases and fumes showed no statistically significant associations with the outcomes. Pack years were inversely associated with FEV_1 %predicted and TL_{CO} %predicted.

Table 2 Relationships between cumulative occupational exposure measures during patients' last four jobs and dependent variables representing lung function impairment and disease-related quality of life (SGRQ) in terms of standardised regression coefficients from unadjusted linear regression analyses

	FEV_1 %predicted	RV/TLC %	TL_{CO} %predicted	SGRQ (score)
Men (n=1283)				
Mineral dust	−0.05	0.07*	−0.01	0.010***
Biological dust	−0.05	0.06*	−0.04	0.10***
Gases and fumes	−0.06*	0.09**	−0.04	0.13***
VGDF	−0.07**	0.11***	−0.05	0.17***
Women (n=759)				
Mineral dust	−0.05	0.09*	−0.06	0.08*
Biological dust	−0.00	−0.02	−0.03	0.03
Gases and fumes	−0.02	0.03	−0.04	0.08*
VGDF	−0.02	0.04	−0.05	0.07

Only complete cases were included (see table 1). N=2042.
*α<0.05, **α<0.01, ***α<0.001.
FEV_1 %predicted, percentage of predicted value of forced expiratory volume in 1 s; RV/TLC %, per cent ratio of residual volume to total lung capacity; SGRQ, St George's Respiratory Questionnaire; TL_{CO} %predicted, percentage of predicted value of transfer factor for carbon monoxide from single-breath measurements; VGDF, vapours, gases, dusts and fumes.

Figure 1A,B visualises the impact of occupational exposures compared with that of cigarette smoking in terms of the magnitude of effects corresponding to interquartile changes in the predictors. In men, effects on FEV_1 %predicted were similar for exposure to gases and fumes and smoking. While effects on quality of life and RV/TLC % were larger for occupational exposure, smoking showed stronger effects on TL_{CO} %. In women, exposure to gases and fumes had similar effects on RV/TLC % as pack years. While smoking had a stronger effect on FEV_1 %predicted and TL_{CO} %predicted, quality of life was slightly more affected by occupational exposure.

To further analyse these results, we employed SEM. Relationship patterns are presented in online supplemental figure S1A,B and tables S4 and S5, indicating that the relationships between functional parameters were similar in men and women, whereas the associations with exposures and comorbidities differed (for detailed results and discussion see online supplemental material).

DISCUSSION

In the present analysis, we used data from a large COPD patient cohort comprising information on lung function, smoking history, comorbidities, disease-related quality of life and up to four previous jobs, allowing for the computation of cumulative occupational exposure to gases and fumes, mineral dust, biological dust and the combination VGDF. This was used to determine the impact of previous occupational exposures on lung function and quality of life in patients with COPD in addition to that of smoking. The results provide novel information on the magnitude of various exposures on various outcomes in COPD and demonstrate persistent effects of occupational exposures despite patients' smoking history.

In men, exposure to gases and fumes predicted small but statistically significant impairments in FEV_1 %predicted, RV/TLC % and TL_{CO} %predicted. The effect of pack years on FEV_1 %predicted was similar to that of exposure to gases and fumes, while it was larger for TL_{CO} %predicted and smaller for quality of life. RV/TLC % was dependent on exposure to gases and fumes only. Among comorbidities, coronary artery disease was linked to FEV_1 %predicted and quality of life. The combined exposure to VGDF showed associations similar to those of exposure to gases and fumes only.

In women, occupational exposure was less frequent and cumulative exposure much lower, except for biological dust. No associations were observed between gases and fumes exposure

Table 3 Adjusted linear regression models of the association between cumulative occupational exposure to gases and fumes during COPD patients' last four jobs and dependent variables representing lung function impairment and disease-related quality of life (SGRQ)

	FEV_1 %predicted		RV/TLC %		TL_{CO} %predicted		SGRQ (score)	
	B	95% CI	B	95% CI	B	95% CI	B	95% CI
Men (n=1283)								
Age (years)	0.17*	(0.03; 0.30)	0.21***	(0.14; 0.29)	−0.02	(−0.17; 0.12)	−0.08	(−0.22; 0.05)
BMI (kg/m^2)	0.66***	(0.43; 0.89)	−0.30***	(−0.43; −0.18)	1.46***	(1.21; 1.71)	0.24*	(0.01; 0.47)
Pack years	−0.03	(−0.05; 0.00)	−0.00	(−0.02; 0.01)	−0.08***	(−0.11; −0.05)	0.01	(−0.02; 0.04)
Diabetes	−1.41	(−4.35; 1.53)	1.27	(−0.30; 2.85)	0.01	(−3.12; 3.14)	0.32	(−2.58; 3.22)
Hypertension	−1.21	(−3.58; 1.16)	−0.04	(−1.32; 1.23)	−0.83	(−3.36; 1.70)	1.47	(−0.87; 3.81)
Coronary artery disease	−3.12*	(−5.78; −0.46)	0.56	(−0.87; 1.99)	−3.80**	(−6.64; −0.96)	8.83***	(6.20; 11.45)
Gases/fumes	−0.03**	(−0.05; −0.01)	0.02***	(0.01; 0.03)	−0.03*	(−0.05; −0.01)	0.05***	(0.03; 0.07)
Women (n=759)								
Age (years)	0.20*	(0.02; 0.39)	0.25***	(0.16; 0.34)	−0.08	(−0.28; 0.12)	−0.01	(−0.19; 0.16)
BMI (kg/m^2)	0.49***	(0.23; 0.75)	−0.27***	(−0.40; −0.14)	1.15***	(0.87; 1.43)	0.41***	(0.17; 0.65)
Pack years	−0.07**	(−0.12; −0.02)	0.02	(−0.01; 0.04)	−0.07*	(−0.12; −0.02)	0.03	(−0.02; 0.08)
Diabetes	1.79	(−4.00; 7.58)	−0.04	(−2.94; 2.86)	−3.48	(−9.78; 2.82)	−0.99	(−6.47; 4.49)
Hypertension	−4.48**	(−7.55; −1.41)	2.10**	(0.56; 3.64)	−2.60	(−5.94; 0.75)	3.45*	(0.54; 6.35)
Coronary artery disease	−1.26	(−6.51; 3.99)	0.76	(−1.87; 3.39)	−3.54	(−9.25; 2.17)	6.09*	(1.12; 11.05)
Gases/fumes	−0.03	(−0.12; 0.06)	0.03	(−0.02; 0.07)	−0.07	(−0.16; 0.03)	0.08	(−0.01; 0.16)

The unstandardised regression coefficients B are mutually adjusted for all variables in the left column. N=2042.
*α<0.05, **α<0.01, ***α<0.001.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1 %predicted, percentage of predicted value of forced expiratory volume in 1 s; RV/TLC %, per cent ratio of residual volume to total lung capacity; SGRQ, St George's Respiratory Questionnaire; TL_{CO} %predicted, percentage of predicted value of transfer factor for carbon monoxide from single-breath measurements.

and quality of life or lung function parameters in the multiple regression models. The relationships between lung function and pack years were similar to those in men, indicating that they were dominated by physiological factors independent of sex. SEM showed that the relationship between lung function, quality of life and smoking was very similar in men and women, while that to occupational exposures differed (see online supplemental material).

Occupational exposures were assessed using the ALOHA JEM.[12–15] Although dependent on patients' recall of their job history, there were robust associations between most exposures and lung function variables. Recall of occupational history agrees well with register data (kappa values 0.65–0.82) regarding person-years in a job, and start/termination dates.[27] Additionally, for this group-based approach via JEM, exposure misclassification is generally expected to be non-differential and potential bias in risk estimates would be minimal, since Berkson error causes little or no bias in the risk estimate but does result in loss of precision.[28 29] This emphasises the usefulness of JEM in clinical-epidemiological analyses such as this one.

The last four jobs available for the present analyses accounted for a median of 30 years (first quartile: 22; third quartile: 40) in men and 26 years (19; 32) in women. As the median age at study participation was 67 (60; 72) years in men and 63 (58; 69) years in women, these four jobs should have accounted for the majority of patients' working life, particularly considering that all were diagnosed with COPD and may not have worked continuously (especially in exposed jobs) until regular retirement age. Moreover, in this cohort's generation, job changes were less usual than nowadays, and women were less likely to continue working after childbirth. However, it cannot be ruled out that early jobs were missing from the analysis, potentially resulting in underestimation of cumulative exposures. Regardless of these limitations, exposure effects were significant and mostly as large as or even greater than those of lifelong smoking history. There were 45 jobs that were associated with high exposure to gases and fumes. The types of exposure differed largely, the most frequent occupations being heavy truck and lorry drivers, motor vehicle mechanics/fitters, painters and related workers, agricultural or industrial machinery mechanics/fitters, and butchers, fishmongers and related food preparers.

The observed effect on RV/TLC % suggests that occupational exposures could affect the lung periphery without having comparable effects on airway obstruction and gas exchange. One reason might be that small changes in peripheral airways induce an elevation of residual volume, which is measured after maximal expiration and thus susceptible to airway collapse. In contrast, FEV_1 measured after deep inspiration needs stronger changes in peripheral airways to be heavily affected, while TL_{CO} is largely determined by the pulmonary capillary blood volume. Regarding lung function one has to consider that the comparison of smoking with occupational exposures might be influenced by smoking cessation after COPD diagnosis, leading to improvement in lung function[30] and thereby reducing the effect of smoking relative to the analysed occupational exposures. The information available was, however, not sufficient to study potential details of smoking history and their residual effects.

Much evidence has been accumulated indicating causal links between occupational exposures and COPD development.[4 31 32] In contrast, the present study analysed associations in patients already diagnosed with COPD. It is noteworthy that the observed associations between occupational exposures and outcomes were consistent with those reported in studies on the risk of developing COPD.[4 31–33] Our finding that not only the risk of development but also the severity of the disease were linked to occupational exposures therefore underlines the importance of workplace hygiene regarding inhalation exposures.

Epidemiological studies suggest that diabetes,[7] hypertension[8] and coronary artery disease[9] are linked to ambient air pollution, in addition to smoking. It is therefore reasonable to investigate whether the occurrence of comorbidities also depends on occupational exposures. In women but not in men, we found

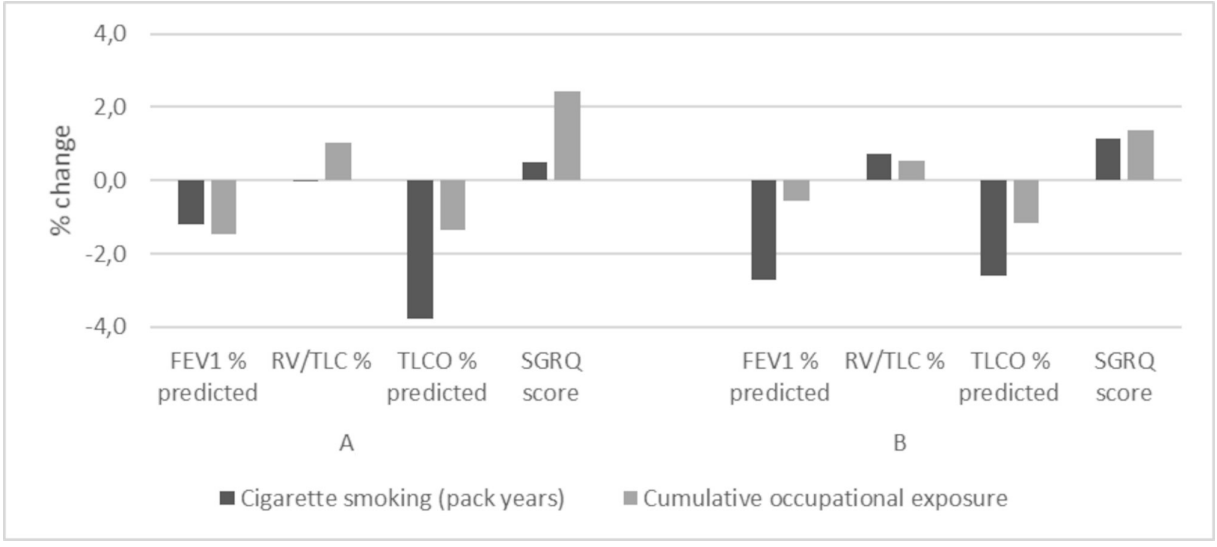

Figure 1 Percentage change in lung function parameters (FEV_1 %predicted, RV/TLC %, TL_{CO} %predicted) and health-related quality of life (SGRQ score) corresponding to interquartile increases in the cumulative occupational exposure to gases and fumes in the patients' last four jobs and to pack years, respectively, in (A) men (n=1283) and (B) women (n=759). The vertical axis shows the changes in %predicted for FEV_1 and TL_{CO}, the changes in RV/TLC expressed as per cent without reference to prediction equations, and for the SGRQ the change in score points. FEV_1 %predicted, percentage of predicted value of forced expiratory volume in 1 s; RV/TLC %, per cent ratio of residual volume to total lung capacity; SGRQ, St George's Respiratory Questionnaire; TL_{CO} %predicted, percentage of predicted value of transfer factor for carbon monoxide from single-breath measurements.

associations between gases and fumes exposure and diabetes, and between VGDF exposure and diabetes and coronary artery disease. There were also associations between coronary artery disease and quality of life (both sexes), FEV_1 %predicted and TL_{CO} %predicted (men only), in line with previous findings in COPD.[34 35] Moreover, hypertension was associated with FEV_1 %predicted, RV/TLC % and quality of life in women. The differences might be related to the fact that coronary artery disease was less prevalent in women, while hypertension was comparably prevalent in women and men.

We also compared the estimated effects of occupational exposure and cigarette smoking, as a reference with well-known impact, using the IQRs of exposures in our cohort. Regarding FEV_1 %predicted as indicator of airway obstruction, the average effect of pack years was weaker than that of occupational exposure to gases and fumes in men but much stronger in women. In contrast, RV/TLC % as indicator of air trapping was predominantly dependent on occupational exposure to gases and fumes in men and more dependent on pack years in women. The finding regarding RV/TLC % is novel. We evaluated this ratio without referring to reference values, as we adjusted for age[36] and BMI in the regression equations. For TL_{CO} %predicted, an indicator of gas exchange capacity, the effect of smoking was markedly larger than that of occupational exposure to gases and fumes in both men and women. As smoking is causally linked to lung emphysema[37] and thus CO diffusing capacity,[38] this result seems plausible. Although emphysema can be linked to specific occupational exposures like mineral dust,[32] it remains unclear which exposures may favour the COPD phenotypes chronic obstructive bronchitis versus emphysema. Importantly, previous occupational exposure to gases and fumes also had persistent effects on quality of life at the time of the study, irrespective of its association with lung function, and this effect was stronger than for smoking, especially in men.

According to the results of the SEM (see online supplemental material), in which all four occupational exposures were included, exposure to gases and fumes exerted direct effects on peripheral airways, and cigarette smoke on alveolar integrity. Correspondingly, TL_{CO} %predicted was linked to exposure to gases and fumes only through its association via RV/TLC % and FEV_1 %predicted. This specific order was a robust result, as the order of lung function measures in the SEM could not be changed without major loss in the goodness of fit. Although SEMs cannot prove causation, they can guide further research regarding the sequence of changes in lung function after occupational exposures. This is a topic which we could not study due to the lack of adequate longitudinal data.

Limitations

This analysis was limited by its cross-sectional design and the retrospective assessment of occupational exposures through questionnaires, with a maximum of four jobs, resulting in a possibly incomplete exposure history. We used the well-established ALOHA JEM but not the most recent extension ALOHA+ and thus cannot exclude the possibility of additional associations in the data. Moreover, the JEM did not consider time-varying aspects of exposures, such as temporal trends that might have been instigated by the strictness of adherence to permissible exposure limits. Consequently, some patients' past exposures might have been underestimated, particularly considering the downward trend in occupational exposure in the Western world.[39] However, it is unlikely that highly exposed jobs would have ranked differently in more recent times compared with jobs with low exposure. Despite potential errors due to incomplete job histories and temporal downward trends in exposure, we found statistically significant robust associations of occupational exposures with lung function impairment and quality of life. However, we limited the analyses to that of separate exposures and did not assess the potential effects of coexposures and interactions. Finally, we did not have sufficient data for adjustment by socioeconomic status, which is a risk factor of COPD and a potential confounder. However, we included smoking as a major confounder often related to socioeconomic status. In principle, the selection of patients who already had developed COPD might have an effect on the relationship between exposures and outcomes, as well as within these variables. It is therefore important to note that we did not address the development of COPD but its phenotype in terms of lung function and comorbidities. Due to the inclusion of GOLD grade 0 patients, the diagnosis of COPD relied on clinical signs, as in previous analyses of COSYCONET data (eg, ref 40), and was not critically dependent on the use of specific spirometric criteria to define airway obstruction.

The strength of our study is that a broad spectrum of COPD severities was included in COSYCONET,[16] moreover, the large sample size and detailed information on lung function and comorbidities, as well as detailed data on patients' job histories that allowed for the calculation of individual indices for cumulative airborne occupational exposure by means of a JEM.

CONCLUSION

In men with COPD, cumulative occupational exposure to gases and fumes was associated with disease-related quality of life and air trapping/lung hyperinflation in terms of RV/TLC %, airway obstruction in terms of FEV_1 %predicted and gas exchange capacity in terms of TL_{CO} %predicted. In women, this type of exposure showed no significant associations when adjusting for confounders. In women and even more so in men, the effect of occupational exposures on current quality of life was larger than that of smoking history. Thus, our data revealed increased lung air trapping and reduced health-related quality of life as previously unrecognised outcomes of occupational exposure to gases and fumes in patients with COPD, in addition to the effects of cigarette smoking. These findings again underline the need for effective workplace hygiene.

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Competing interests DN received honoraria for lectures from Bristol Myers Squibb, Berlin Chemie, Boehringer Ingelheim, Chiesi, GlaxoSmithKline (GSK), Mundipharma, Novartis, Hexal and Lilly. Moreover, he received payments for expert testimony from courts and social accident insurances and institutional travel support from LMU Munich and reports personal stocks (mixed). SK received grants (82DZL083B2) from the German Center for Lung Research (DZL). Within the past 36 months, CV received grants or contracts from the German Ministry of Education and Science (BMBF) and from AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, GSK, Grifols and Novartis. Moreover, he received consulting fees from Aerogen, AstraZeneca, Boehringer Ingelheim, CSL Behring, Chiesi, GSK, Insmed, Menarini, Novartis and Nuvaira, and payments for lectures, presentations, speaker bureaus, manuscript writing or educational events from Aerogen, AstraZeneca, Boehringer Ingelheim, CSL Behring, Chiesi, GSK, Insmed, Menarini, Novartis, Roche and Sanofi. UO is the chair of the Committee for Maternity Protection (Ausschuss für Mutterschutz), Bundesministerium für Familie, Senioren, Frauen und Jugend (BMFSFJ). She received payments from GSK for a lecture on vaccination in health settings, from Sozial- und Arbeitsmedizinische Akademie Baden-Württemberg (SAMA) for a lecture on maternity protection and from Akademie für Gesundheit und Lebensmittelsicherheit im Bayerischen Landesamt für Gesundheit und Lebensmittelsicherheit for a lecture on maternity protection. She received support for attending meetings/travel from BMJSFJ and from the LMU University Hospital, LMU Munich. HK is the editor-in-chief of Occupational and Environmental Medicine.

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Ethics approval COSYCONET has been approved by the ethics committees of all study centres, was performed in accordance with the Declaration of Helsinki and was registered at ClinicalTrials.gov (NCT01245933). The list of study centres is available at http://www.asconet.net/html/cosyconet/studzent. Participants gave informed consent to participate in the study before taking part.

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