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The impact of occupational exposure to crystalline silica dust on respiratory function (airway obstruction and FEF_{25-75}) in the French general population

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ABSTRACT

Introduction: Although several studies have studied the relationship between occupational exposure to crystalline silica dust and respiratory mortality, few have examined the relationship with impairments in respiratory function and the exposure threshold triggering spirometric monitoring in exposed workers. The objective of the present study was to evaluate the impact of exposure to crystalline silica dust on respiratory function.

Methods: We included 1428 male participants (aged 40 to 65) recruited from the French general population, at random from electoral rolls, in the cross-sectional ELISABET study and for whom data on forced expiratory flow-volume curve indices z-scores (calculated using the Global Lung Function Initiative 2012 equations) and exposure (via a questionnaire) were available. A cumulative exposure index (CEI) for crystalline silica dust (CEI_{silica}, expressed in $mg.m^{-3}$.year) was calculated using the Matgéné occupational exposure matrix.

Results: 293 of the 1428 participants (20.52%) reported exposure to silica dust. We found that the adjusted z-scores for the forced expiratory volume in the first second/forced vital capacity (FEV_1/FVC) ratio decreased significantly as CEI_{silica} increased. After adjustment, the adjusted z-scores for FEV_1/FVC (β: −0.426 (95% confidence interval (CI): −0.792, −0.060) per 1 mg m^{-3}.year increment) and the mean forced expiratory flow between 25 and 75% of the forced vital capacity (FEF_{25-75}) (β: −0.552 (95% CI: −0.947, −0.157)) were significantly lower in the participants with CEI_{silica} ≥1 mg m^{-3}.year than in non-exposed participants. The likelihoods of having airway obstruction (odds ratio (OR): 3.056 (95% CI: 1.107, 7.626)) or having an impaired FEF_{25-75} (OR: 4.305 (95% CI: 1.393, 11.79)) were also significantly higher in participants with CEI_{silica} ≥1 mg m^{-3}.year.

Conclusion: Our results emphasize the importance of spirometry-based monitoring in workers exposed to more than 1 mg m^{-3}.year of crystalline silica dust, in order to identify small airway obstruction or airway obstruction as early as possible.

1. Introduction

Crystalline silica is naturally present in rocks, sand, and soils. Quartz is the most frequently encountered type of crystalline silica, followed by cristobalite and tridymite. Breathing crystalline silica dust is known to cause silicosis (whether acute, accelerated or chronic), bronchial and/or lung cancer (especially in patients with chronic silicosis: crystalline silica dust is listed as a category 1 carcinogen by the International Agency for Research on Cancer (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012)), auto-immune diseases (e.g. systemic scleroderma and rheumatoid arthritis), and non-malignant respiratory tract diseases. (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012; Leung et al., 2012) A recent report from the US Occupational Safety and Health Administration indicated

Abbreviations: AO, Airway obstruction; CEI, Cumulative exposure index; CEI_{silica}, Cumulative exposure index for crystalline silica dust; d_{ae}, Aerodynamic diameter; ECSC-93, European Steel and Coal Community 1993 reference equations; GLI-2012, Global Lung Function Initiative 2012 reference equations for spirometry; JEM, Job-exposure matrix; OEL, Occupational exposure limit; PY, Pack-years.

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that there is a dose-effect relationship between exposure to crystalline silica dust and a decline in respiratory function (OSHA, 2016). This decline can trigger the onset of airway obstruction (AO), even in the absence of silicosis. AO can also result from silicosis - the mechanisms, outcomes and dose-effect relationship of which have been well characterized (Anses, 2019).

The Institute of Occupational Medicine estimates that about 5,300,000 workers in the European Union (i.e. around 2.6% of the labour force) were potentially exposed to silica in 2006 (Institute of Occupational Medicine, 2011). About 2.3 million workers in the United States (i.e. around 1.5% of the labour force) were potentially exposed in 2012 according to the US Occupational Safety and Health Administration estimates (OSHA, 2016). In France, exposure to crystalline silica dust concerned at least 358,400 salaried employees (men: 94.6%) (1.47% of the total salaried workforce, according to French national data for 2017) (Matinet et al., 2020). This number is very probably an underestimate, given (i) the self-reported nature of the data on occupational exposure during the week preceding the statutory annual medical check-up for salaried employees, and (ii) the occupational physicians' imprecise knowledge of actual occupational exposure. Several professions have a particularly high likelihood of exposure to crystalline silica dust; they include construction workers, workers installing work surfaces made of artificial stone, miners, quarry workers, stonemasons cutting or polishing siliceous stones, workers building or repairing industrial ovens made of refractory bricks, and glassworkers. According to the ANSES report, an estimated 8% of salaried employees are exposed to levels of crystalline silica dust above France's current occupational exposure limit (OEL) of 0.1 mg m^{-3}, and 20% are exposed to levels above the OEL of 0.025 mg m^{-3} recommended by the American Conference of Governmental Industrial Hygienists.

The ANSES report referred to the conclusions of Hoet et al.'s systematic literature review (Hoet et al., 2017) and stated that there is currently not enough evidence to define a crystalline silica dust exposure threshold associated with an elevated likelihood of impaired respiratory function. The great majority of studies of the decline in respiratory function seen after exposure to crystalline silica dust had cross-sectional or longitudinal case-control designs. Most of these studies focused on the forced vital capacity (FVC), the forced expired volume in the first second (FEV_1), and the FEV_1/FVC ratio, whereas very few assessed the forced expiratory flow between 25% and 75% of the FVC ($FEF_{25\text{-}75}$). In fact, some researchers have shown that a decrease in $FEF_{25\text{-}75}$ is a marker of early bronchial obstruction (Hogg et al., 2004; McDonough et al., 2011; Polverino and Soriano, 2020; Stockley et al., 2017b; Usmani et al., 2021). Moreover, this type of study is generally performed on populations of people in work, which typically gives rise to a "healthy worker" effect (Eisen et al., 1995). The French High Authority for Health (*Haute Autorité de Santé*, HAS)'s good practice guidelines on the occupational health monitoring of workers currently or previously exposed to crystalline silica dust (Hulo et al., 2021) defined a threshold of 1 mg m^{-3}.year for high exposure to silica, which then triggers closer monitoring of flow-volume curves in exposed employees (starting 10 years after the start of the exposure and then every 2 years, vs. 20 years after the start and then every 4 years for intermediate exposure (<1 mg m^{-3}.year)). Some researchers have suggested exposure thresholds to be used as a criterion for diagnosing occupational chronic obstructive pulmonary disease (COPD), for example in Germany (Möhner and Nowak, 2020), but to our knowledge, no other country has set an exposure threshold triggering spirometric monitoring in exposed workers.

The objective of the *Enquête Littoral Souffle Air Biologie Environnement* (ELISABET) cross-sectional study was to compare the prevalence of AO in two urban areas in northern France: one with exclusively urban pollution (Lille) and the other with mixed urban and industrial pollution (Dunkirk). The ELISABET study participants were recruited from the general population (Quach et al., 2015).

The objective of the present analysis was to evaluate the impact of exposure to crystalline silica dust on forced expiratory flow-volume curve indices in a subset of the ELISABET study participants.

2. Methods

2.1. Study design and population

The study participants were men aged 40 to 65 having participated in the ELISABET cross-sectional study between January 2011 and November 2013. The methodology of the ELISABET study has been described in detail elsewhere (Chérot-Kornobis et al., 2018; Clement et al., 2017; Dauchet et al., 2018; Devien et al., 2018; Giovannelli et al., 2018; Havet et al., 2020; Quach et al., 2015; Riant et al., 2018). Briefly, all the participants had lived in the same city or the surrounding urban area (either Lille or Dunkirk) for at least the 5 years immediately prior to inclusion. The participants were selected at random from electoral rolls, with stratification for sex, age, and city area (Lille or Dunkirk). We excluded ELISABET study participants who lacked acceptable spirometry data, female participants because prevalence of exposure were too low in this group for valid statistical analysis, and participants for whom occupational exposure to crystalline silica dust could not be quantified.

2.2. Data collection

Data were collected by a trained, registered nurse who interviewed each participant about respiratory symptoms, tobacco consumption and job titles for the career history. The nurse then performed spirometry testing.

2.2.1. General characteristics

With regard to the participants' clinical data, a history of asthma was defined as an answer of "yes" to the question "Have you been diagnosed with asthma by a physician?". Respiratory symptoms included a chronic cough (defined as a persistent cough for more than 3 months a year), chronic bronchitis (defined as persistent phlegm production for more than 3 months a year), and dyspnoea (evaluated on the five-point modified Medical Research Council (mMRC) scale, ranging from the absence of dyspnoea (grade 0) to nearly total incapacity (grade 4)) (Mahler and Wells, 1988). In our study, the presence of dyspnoea was defined as mMRC grade 3 (stops for breath after walking 100 yards or after a few minutes on level ground) or grade 4 (too breathless to leave the house, or breathless when dressing or undressing). Tobacco use status was defined in three categories: current smokers (at least one cigarette a day for the last year); former smokers (having giving up smoking more than 3 months previously and having smoke at least one cigarette a day for at least a year), and never-smokers (neither current nor former smoker).

2.2.2. Spirometry data

The spirometry indices included FEV_1, FVC, the FEV_1/FVC ratio, and $FEF_{25\text{-}75}$. Spirometry was performed using Micro 6000 devices (Medisoft, Belgium) calibrated weekly. The measurements complied with the 2005 joint American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Miller et al., 2005) and were validated by a qualified engineer. The spirometry indices were adjusted for age and sex by using the Global Lung Function Initiative (GLI) 2012 reference equations (Quanjer et al., 2012). No reversibility test was performed. The spirometry results were expressed as a percentage of the value predicted by the GLI-2012 equation (% predicted) and as a z-score (defined as the number of standard deviations between the GLI-2012 % predicted and the measured value, after adjustment for sex, age, and height). The presence of AO was defined by a GLI-2012 z-score for the FEV_1/FVC ratio more negative than -1.645, and an impaired $FEF_{25\text{-}75}$ was defined as a GLI-2012 z-score more negative than -1.645.

2.2.3. Occupational exposure

2.2.3.1. Career history. Each participant was asked during the face-to-face interview about his first job, his latest job, the job that he had done for the longest during his career, and the various jobs that might have led to exposure to vapours, gases, fumes and/or dust. The start year and end year were noted for each job. Each job (defined as a profession exercised in a given sector of activity (Groupe de travail Matgéné, 2010)) was coded by combining a level 4 PCS-2003 professional/socioprofessional code (Institut national de la statistique et des études économiques, 2003) and a level 5 NAF-2008 economic activity code. (Institut national de la statistique et des études économiques, 2008) PCS-2003 and NAF-2008 are French classifications of professions and sectors of activity, respectively.

2.2.3.2. Exposure to crystalline silica dust. Each participant's exposure to crystalline silica dust was quantified as a cumulative exposure index (CEI_{silica}) for each job and for the career as a whole, using the French job-exposure matrix (JEM) Matgéné created by *Santé Publique France* (Delabre et al., 2010; Févotte et al., 2011; Groupe de travail Matgéné, 2010). For each occupation (identified by the French national NAF-2008 and PCS-2003 codes), this JEM provides (i) the probability of exposure, (ii) the frequency of exposure, and (iii) the intensity of exposure for one or more periods between 1947 and 2019. The CEI was calculated as follows: CEI_{silica} = *probability* x *intensity* x *frequency* x *duration*. The probability was defined as the percentage of workers in that occupation exposed to crystalline silica dusts. The intensity was defined as the concentration to which a worker is exposed (depending on the work environment and the tasks performed), in four categories: 0.02–0.1 mg m^{-3}, 0.1–0.5 mg m^{-3}, 0.5–1 mg m^{-3}, and >1 mg m^{-3}. In our analysis, the median value in each class was used, i.e. 0.06 mg m^{-3}, 0.3 mg m^{-3}, 0.75 mg m^{-3}, and 1.5 mg m^{-3}. The frequency corresponding to the time spent on tasks with exposure, expressed as a percentage of the total working time (Delabre et al., 2010; Févotte et al., 2011; Groupe de travail Matgéné, 2010). Lastly, the duration corresponding to the time (in years) spent in the job in question. When a participant's job covered several periods of time in the JEM, the CEI_{silica} was calculated for each period. The CEI_{silica} for the career as a whole was calculated by summing the CEI_{silica} values for each job.

2.2.3.3. Other occupational exposures. We looked for other occupational exposures that might be related to respiratory disorders. Based on the pairs of NAF-2008/PCS-2003 codes and for each job, we evaluated exposure to vapours (molecules or liquid particles in suspension in the air, generated from a liquid), gases (molecules in suspension in the air under normal temperature and atmospheric pressure conditions), fumes (dispersions of very fine solid particles (aerodynamic diameter (d_{ae}) < 4.25 μm) generated by thermal processes (either by condensation from the gaseous phase or by incomplete combustion) or generated by gas-phase reactions (e.g. the reaction between ammonia and hydrogen chloride)), and dusts other than crystalline silica (dispersions of solid particles (d_{ae} > 10 μm) in the atmosphere, formed by a mechanical process or by resuspension from deposits).

The absence of a published JEM suitable for use in France with the NAF-2008 and PCS-2003 codes for these vapours, gases, fumes and dusts (other than crystalline silica) prompted us to create new ones for the present study. The maximum level of exposure to each of these harmful substances was estimated by two occupational physicians, with expertise in the relationship between occupational exposure and health, according to the NAF-2008 and PCS-2003 codes and the exposure data to vapours, gases, fumes and dusts reported by the participants during the face-to-face interview. Firstly, for each harmful substance (vapours, gases, fumes and dusts) the exposure associated with each NAF-2008 code was rated as "no exposure" (level 0), "low exposure" (level 1) or "high exposure" (level 2). Secondly, the exposure associated with each PCS-2003 code was rated as "no exposure" (level 0), "low exposure" (level 1) or "high exposure" (level 2). For each participant and each of the participant's jobs, the CEIs for the four harmful substances were calculated by multiplying the level of exposure associated with the NAF-2008 code by the level of exposure associated with the PCS-2003 code and by the duration of the job concerned. The consistency of the exposure assessment for each pair of NAF-2008/PCS-2003 codes was checked so that, for example, a PCS-2003 rated as "high exposure" (level 2) could not be associated with a NAF-2008 rated as "no exposure" (level 0) for a given substance unless this situation was indeed realistic. The CEI for the career as a whole was calculated by summing the CEIs for each job.

2.3. Statistical analysis

Participants exposed to silica and those not exposed were compared using a chi-squared test (or Fisher's exact test, if the conditions for valid application of a chi-squared test were not met) for qualitative variables and Student's t-test (or the Mann-Whitney test, if the data were not distributed symmetrically) for continuous, quantitative variables. The distribution of quantitative variables was checked by the visual inspection of a histogram and a density curve. We applied the multiple imputation by chained equations method to the missing data for bodyweight (6 (0.4%) subjects with missing data) and tobacco use (pack-years, PY) (27 (1.9%) subjects with missing data).

The relationship between the CEI_{silica} and the GLI-2012 z-score for the FEV_1/FVC ratio was studied using a linear regression model. A similar model was used to study the relationship between the CEI_{silica} value and the respective GLI-2012 z-scores for $FEF_{25\text{-}75}$, FEV_1 and FVC.

A logistic regression model was built in order to calculate the odds ratio (OR) and its 95% confidence interval (CI) for the likelihood of having AO as a function of the CEI_{silica} value. A logistic regression model was also used to study the relationship between an impaired $FEF_{25\text{-}75}$ and the CEI_{silica}.

The unadjusted logistic and linear regression models (model 0) were adjusted in two steps. The first model (model 1) was adjusted for the participants' general characteristics only: age, body mass index (BMI), the season during which the spirometry indices were measured, tobacco use status, a history of asthma, and the city area. The second model (model 2) was the same as model 1 but was additionally adjusted for other occupational exposures (the CEIs for vapours, gases, fumes, and dusts other than silica).

In order to detect a possible threshold effect for exposure to silica ≥1 mg m^{-3}.year, the various logistic and linear regression models were repeated after transformation of the continuous CEI_{silica} variable into a three-category variable: "non-exposed" (the reference), "exposure <1 mg m^{-3}.year", and "exposure ≥1 mg m^{-3}.year". We chose a 1 mg m^{-3}.year threshold because this value is used to define high exposure in the HAS's good practice guidelines for the occupational health monitoring of workers exposed to or having been exposed to crystalline silica dust (Hulo et al., 2021).

We performed sensitivity analyses by repeating the linear and logistic regressions of the $FEF_{25\text{-}75}$ data in a subsample of participants with an FVC z-score more negative than −1.645. All statistical analyses were performed with R software (version 4.1.0). (R Core Team, 2013).

2.4. Ethical aspects

The study protocol was registered at ClinicalTrials.gov (identifier: NCT02490553) and had been approved by the local independent ethics committee (*CPP Nord Ouest IV*, Lille, France; reference: 2010-A00065-34), in compliance with the French legislation on biomedical research. All the participants gave their written, informed consent prior to inclusion in the study.

3. Results

3.1. Population

In total, 3275 people had been included in the ELISABET study. Data on 1428 men were analyzed in the present study (Fig. 1). Fourteen participants (1%) lacked FEF_{25-75} data, and so the FEF_{25-75} analysis covered 1414 participants.

3.2. General characteristics, spirometry data, and occupational exposure as a function of exposure to crystalline silica dust

The prevalence of exposure to crystalline silica dust in our study population was 20.52% (293 out of 1428). The participants exposed to silica did not differ significantly from the non-exposed participants with regard to any of the general characteristics except tobacco use (the median number of PY was significantly higher in the exposed participants (19 PY) than in the non-exposed participants (15.2 PY; p = 0.022)) and city area (14% of participants living in Lille area were exposed and 27% in Dunkirk area; p < 0.0001)) (Table 1). In the study population as a whole, the prevalence of AO was 12.3% (176 out of 1428) and the prevalence of an impaired FEF_{25-75} was 7.7% (110 out of 1428). The proportion of participants presenting with AO was slightly higher in the exposed group (13.3%) than in the non-exposed group (12.1%), although this difference was not statistically significant (p = 0.565). The proportion of participants presenting an impaired FEF_{25-75} value was higher in the exposed group (8.9%) than in the non-exposed group (7.4%), although the difference was again not significant (p = 0.398). We did not observe a significant difference between the exposed and non-exposed groups with regard to the spirometry indices (whether expressed as a z-score or as % predicted).

In the participants exposed to crystalline silica dust, the median (interquartile range (IQR)) CEI_{silica} was 0.135 (IQR: 0.0351, 0.420) mg. m^{-3}.year, and 31 participants (10.6%) had a CEI greater than or equal to 1 mg m^{-3}.year (Table 2). Participants exposed to silica were more frequently exposed to vapours, gases and fumes and had higher CEIs for these substances. Participants not exposed to crystalline silica dust had a higher median CEI and a greater median duration of exposure to dusts (other than crystalline silica dust).

The analysis of the CEI_{silica} in three classes (not exposed, and exposed above and below a threshold of 1 mg m^{-3}.year) showed that the median CEI_{silica} in participants exposed below 1 mg m^{-3}.year (n = 262) was 0.116 (IQR: 0.0313, 0.299) mg.m^{-3}.year and 2.16 (IQR: 1.46, 3.00) mg. m^{-3}.year in participants with a CEI_{silica} greater than or equal to 1 mg m^{-3}.year (n = 31).

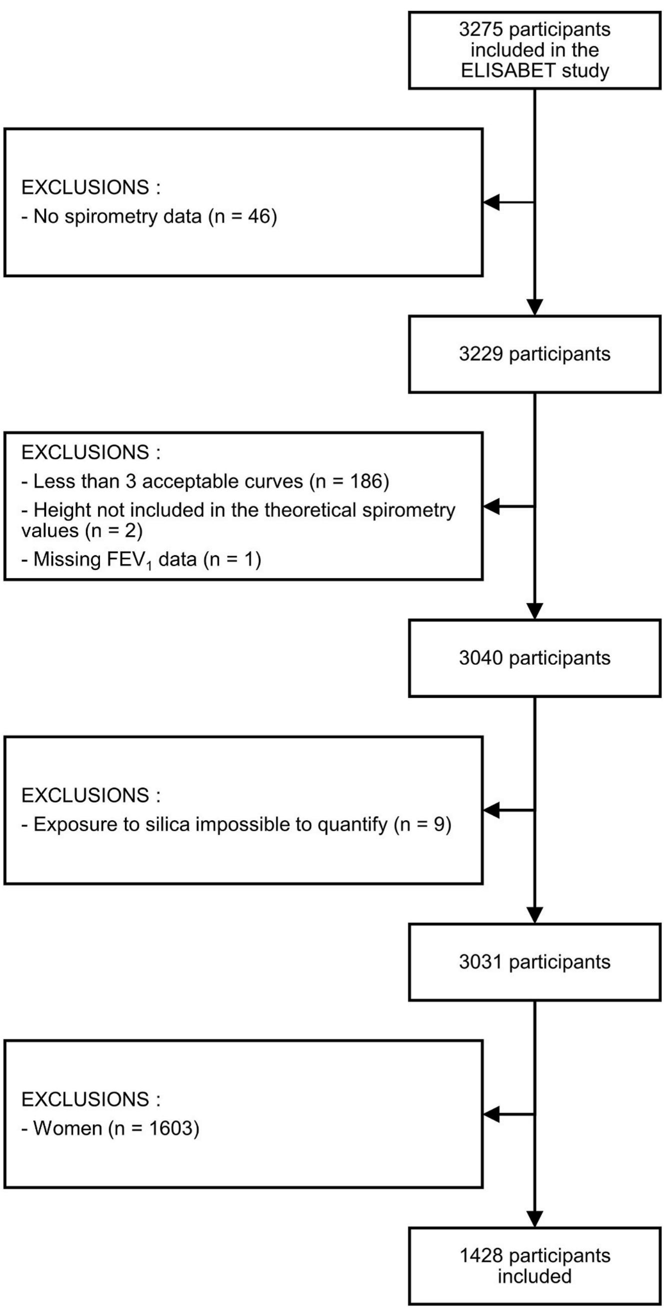

Fig. 1. Study flow chart. FEV1: forced expiratory volume in the first second.

3.3. Association between the z-scores for the FEV_1/FVC ratio or FEF_{25-75} and the CEI_{silica}

We observed a significant decrement in the FEV_1/FVC z-score as the CEI_{silica} (mg.m^{-3}.year) increased (β: −0.114 (95% CI: −0.223, −0.005) per 1 mg m^{-3}.year increment) (Table 3). This association persisted after adjustment for general characteristics (model 1) (β: −0.112 (95% CI: −0.216, −0.007)) and for occupational co-exposure (model 2).

Similar results were found for the FEF_{25-75} z-score in the non-adjusted model (β: −0.154 (95% CI: −0.271, −0.037)) and in the models adjusted for general characteristics (model 1) (β: −0.142 (95% CI: −0.253, −0.031)) and for occupational co-exposure (model 2) (β: −0.162 (95% CI: −0.278, −0.046)).

An analysis of the CEI_{silica} in three classes did not reveal a significant association between the value of the FEV_1/FVC z-score and a CEI_{silica} below 1 mg m^{-3}.year, relative to non-exposed participants and regardless of the adjustment (Table 4). In contrast, the FEV_1/FVC z-score was significantly lower among participants with a CEI_{silica} greater than or equal to 1 mg m^{-3}.year than among non-exposed participants in model 2 only (the model adjusted for both occupational exposure and general characteristics: β: −0.426 (95% CI: −0.792, −0.060)).

Likewise, the FEF_{25-75} z-score was significantly lower in participants with a CEI_{silica} greater than or equal to 1 mg m^{-3}.year (β: −0.484 (95% CI: −0.879, −0.089)). The association persisted after adjustment for general characteristics (model 1) (β: −0.424 (95% CI: −0.800, −0.048)) and occupational co-exposure (model 2) (β: −0.552 (95% CI: −0.947, −0.157)). The association was also observed for the participants with a CEI_{silica} below 1 mg m^{-3}.year, albeit only in the model adjusted for occupational co-exposure (model 2) and with a smaller decrement in the z-score (β: −0.191 (95% CI: −0.358, −0.025)).

The splines describing the relationship between the CEI_{silica} in mg. m^{-3}.year and the FEV_1/FVC z-score or the FEF_{25-75} z-score suggest that the relationship were linear and so did not evidence a CEI threshold beyond which respiratory function decreased.

The analysis assessing the relationship between the CEI_{silica} and the GLI-2012 z-score for the FEV_1 and the FVC are shown in the appendices

Table 1
General characteristics and spirometry indices as a function of exposure to crystalline silica dust.

Variables		TOTAL	Exposure to silica		p-value
			Non-exposed	Exposed	
		(*n* = *1428*)	(*n* = *1135*)	(*n* = *293*)	
GENERAL CHARACTERISTICS					
Age (years)		54.2 (47.7, 59.8)	54.2 (47.5, 59.8)	54.2 (48.3, 59.5)	0.971
Height (cm)		176 ± 6.68	176 ± 6.60	176 ± 7.00	0.237
Bodyweight (kg)		85.7 ± 14.5	85.4 ± 14.2	86.8 ± 15.8	0.131
BMI (kg/m^2)		27.7 ± 4.38	27.5 ± 4.28	28.2 ± 4.73	0.033
	Normal weight (<25 $kg\ m^{-2}$)	401 (28.1%)	324 (28.5%)	77 (26.3%)	0.177
	Overweight	677 (47.4%)	545 (48.0%)	132 (45.1%)	
	Obese (≥30 $kg\ m^{-2}$)	350 (24.5%)	266 (23.4%)	84 (28.7%)	
Tobacco use status	Never smoker	537 (37.6%)	442 (38.9%)	95 (32.4%)	0.07
	Former smoker	585 (41.0%)	461 (40.6%)	124 (42.3%)	
	Current smoker	306 (21.4%)	232 (20.4%)	74 (25.3%)	
Tobacco use in PY		16.0 (7.55, 30.0)	15.2 (7.30, 29.0)	19.0 (10.0, 32.4)	0.022
City area	Lille	729 (51.1%)	627 (55.2%)	102 (34.8%)	<0.0001
	Dunkirk	699 (48.9%)	508 (44.8%)	191 (65.2%)	
History of asthma		137 (9.6%)	117 (10.3%)	20 (6.8%)	0.071
Chronic cough		139 (9.7%)	105 (9.3%)	34 (11.6%)	0.226
Chronic bronchitis		58 (4.1%)	45 (4.0%)	13 (4.4%)	0.715
Dyspnoea		22 (1.5%)	16 (1.4%)	6 (2.0%)	0.427
SPIROMETRY INDICES					
AO		176 (12.3%)	137 (12.1%)	39 (13.3%)	0.565
Impaired FEF_{25-75}[a]		110 (7.7%)	84 (7.4%)	26 (8.9%)	0.398
FVC	z-score	0.0406 ± 1.03	0.0644 ± 1.01	−0.0514 ± 1.10	0.086
	% predicted.	101 ± 14.3	101 ± 14.0	99.3 ± 15.2	0.079
FEV_1	z-score	−0.256 ± 1.17	−0.228 ± 1.15	−0.366 ± 1.23	0.071
	% predicted.	96.1 ± 16.4	96.5 ± 16.1	94.4 ± 17.6	0.053
FEV_1/FVC		0.749 ± 0.0756	0.750 ± 0.0746	0.745 ± 0.0790	0.287
	z-score	−0.512 ± 1.02	−0.497 ± 1.02	−0.570 ± 1.01	0.275
	% predicted.	95.2 ± 9.43	95.4 ± 9.31	94.7 ± 9.88	0.255
FEF_{25-75}[a]	z-score	−0.0333 ± 1.09	−0.0068 ± 1.08	−0.136 ± 1.11	0.716
	% predicted.	102 ± 36.2	103 ± 36.4	98.8 ± 35.2	0.069
Season	Spring-summer	735 (51.5%)	593 (52.2%)	142 (48.5%)	0.248
	Autumn-winter	693 (48.5%)	542 (47.8%)	151 (51.5%)	

Note: Data are presented as the n (%), mean ± standard deviation, or median (interquartile range). BMI: body mass index; PY: pack-years; AO: airway obstruction (defined as a GLI-2012 z-score for FEV1/FVC < −1.645); FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; FEF25-75: mean forced expiratory flow between 25 and 75% of the FVC (impairment was defined as a GLI-2012 z-score < −1.645). Comparison of quantitative variables as a function of exposure to silica: Student's t-test (except for age: the Mann-Whitney test). Comparison of qualitative variables as a function of exposure to silica: a chi-squared test (except for dyspnoea: Fisher's exact test). The results for tobacco use in PY are presented for former smokers and current smokers only (n = 891).

[a] 14 (1%) missing data for the FEF_{25-75} (including 3 in the exposed group).

(Table A1 and A2).

3.4. Association between the presence of AO or an impaired FEF_{25-75} with CEI_{silica}

We did not observe a significant association between the CEI_{silica} (in $mg.m^{-3}$.year) and the presence of AO, regardless of whether or not the model was adjusted (Table 5). Similar results were observed for an impaired FEF_{25-75} both before and after adjustment.

The use of the CEI_{silica} in three classes revealed a significant increment in the likelihood of presenting AO for exposure to silica ≥1 mg m^{-3}.year (relative to non-exposed participants) but only in the model adjusted for occupational co-exposure (model 2) (OR: 3.056 (95% CI: 1.107, 7.626)). The association was not found for the participants with exposure below 1 mg m^{-3}.year, relative to non-exposed participants and regardless of adjustment.

We also observed a significant increment in the likelihood of presenting an impaired FEF_{25-75} for exposure to silica ≥1 mg m^{-3}.year (relative to non-exposed participants) in the non-adjusted model (OR: 3.095 (95% CI: 1.122, 7.325)) or after adjustment for general characteristics (model 1) (OR: 3.237 (95% CI: 1.128, 8.064)) or occupational co-exposure (model 2) (OR: 4.305 (95% CI: 1.393, 11.79)) (Table 6). We did not observe a significant association for participants with exposure below 1 mg m^{-3}.year (relative to the non-exposed participants), with or without adjustment.

3.5. Analyses of FEF_{25-75} in the participants with a normal FVC

In the 1414 participants with data for FEF_{25-75}, 1354 (95.76%) had a normal FVC. Of these, 272 (20.09%) were exposed to crystalline silica dust. We observed a significant decrement in the FEF_{25-75} z-score as the CEI_{silica} in $mg.m^{-3}$.year increased but only after adjustment for occupational exposure (model 2) (−0.119 (95% CI: −0.234, −0.005) for a 1 mg m^{-3}.year increment in the CEI_{silica}). We did not observe a significant association between the FEF_{25-75} z-score and the CEI_{silica} in classes (above or below the threshold at 1 mg m^{-3}.year threshold) before or after adjustment. Furthermore, we did not observe a significant association between the presence of an impaired FEF_{25-75} and the CEI_{silica} as a continuous variable (in $mg.m^{-3}$.year) or a categorical variable (with a threshold at 1 mg m^{-3}.year) in participants with a normal FVC, both before and after adjustment.

4. Discussion

In our sample of 1428 men, the prevalence of exposure to crystalline silica dust was 20.52% (n = 293) (14% in Lille and 27% in Dunkirk). 12.3% (n = 176) of the participants presented AO, and 7.7% (n = 110) presented an impaired FEF_{25-75}. After adjustment for various factors (including tobacco use status and occupational co-exposure to vapours, gases, fumes, and dusts other than silica), the FEV_1/FVC and FEF_{25-75} z-scores fell significantly as the CEI_{silica} increased. We observed a significant decrement in the FEF_{25-75} z-score as the CEI_{silica} in $mg.m^{-3}$.year

Table 2
Occupational exposure to vapours, gases, fumes and dusts, as a function of exposure to crystalline silica dust.

Work-related exposure		TOTAL	Exposure to silica		p-value
			Non-exposed	Exposed	
		(*n* = *1428*)	(*n* = *1135*)	(*n* = *293*)	
Silica	CEI (mg. m^{-3}.year)[a]	0.135 (0.035, 0.420)	–	0.135 (0.035, 0.420)	
	Duration (years)[a]	19.0 (6.00, 30.0)	–	19.0 (6.00, 30.0)	–
	CEI ≥1 mg m^{-3}.year[a]	31 (2.2%)	–	31 (10.6%)	–
Vapours	Exposed (yes)	709 (49.6%)	463 (40.8%)	246 (84.0%)	<0.0001
	CEI (u. year)[a]	28.0 (11.0, 43.0)	25.0 (9.00, 39.0)	30.0 (16.0, 52.0)	0.0003
	Duration (years)[a]	21.0 (8.00, 33.0)	20.0 (7.00, 33.0)	23.0 (11.0, 33.0)	0.061
Gases	Exposed (yes)	505 (35.4%)	293 (25.8%)	212 (72.4%)	<0.0001
	CEI (u. year)[a]	30.0 (12.0, 60.0)	28.0 (9.00, 46.0)	40.0 (18.5, 70.0)	<0.0001
	Duration (years)[a]	20.0 (7.00, 33.0)	18.0 (7.00, 33.0)	21.0 (9.75, 33.0)	0.106
Fumes	Exposed (yes)	727 (50.9%)	462 (40.7%)	265 (90.4%)	<0.0001
	CEI (u. year)[a]	31.0 (12.0, 56.0)	26.0 (11.0, 43.0)	42.0 (18.0, 70.0)	<0.0001
	Duration (years)[a]	22.0 (8.00, 33.0)	20.0 (7.00, 33.0)	25.0 (10.0, 33.0)	0.176
Dusts[b]	Exposed (yes)	636 (44.5%)	519 (45.7%)	117 (39.9%)	0.075
	CEI (u. year)[a]	28.5 (12.0, 54.5)	33.0 (14.0, 60.0)	18.0 (5.00, 32.0)	<0.0001
	Duration (years)[a]	20.0 (7.00, 32.0)	22.0 (9.00, 34.0)	10.0 (3.00, 20.0)	<0.0001

Note: Data are presented as the n (%) or median (interquartile range). CEI: cumulative exposure index. Comparison of quantitative variables as a function of exposure to silica: the Mann-Whitney test. Comparison of qualitative variables as a function of exposure to silica: a chi-squared test.
[a] Solely in participants exposed to the substance in question.
[b] Dusts other than silica.

increased, after adjustment for occupational exposure in participants with a normal FVC. We also evidenced a significant decrement in the FEV_1/FVC z-score (after adjustment) in the participants with a CEI_{silica} ≥1 mg m^{-3}.year (relative to non-exposed participants), whereas the association was not significant for exposed participants with a CEI below this threshold. The FEF_{25-75} z-score was also significantly lower (after adjustment) in participants with a CEI_{silica} ≥1 mg m^{-3}.year and, to a lesser extent, those with a CEI below 1 mg m^{-3}.year, relative to non-exposed participants. The likelihood of presenting AO was significantly greater only in the participants with a CEI_{silica} ≥1 mg m^{-3}.year, relative to the non-exposed participants (OR: 3.056 (95% CI: 1.107, 7.626)). A similar result was found for the likelihood of presenting an impaired FEF_{25-75} for CEI_{silica} ≥1 mg m^{-3}.year (OR: 4.305 (95% CI: 1.393, 11.79)).

4.1. Prevalence of exposure

The prevalence of exposed to crystalline silica dust was markedly higher in our study population (14% in Lille and 27% in Dunkirk) than in the workforce in general (1.4%, according to the 2017 SUMER survey) or among all male employees (2.7%) (Matinet et al., 2020). This difference might be due to the SUMER survey's data collection methods: reporting by the occupational physician might have underestimated exposure to silica, whereas our evaluation (based on the Matgéné JEM) was less subjective. Furthermore, the SUMER figure corresponds to the proportion of participants exposed at the time of the survey, rather than the whole-career prevalence of exposure. The episodes of silica exposures recorded in our study covered most of the participants' career; the participants were aged between 40 and 65 at the time of the survey (2011–2013). On the national level, the prevalence of exposure to silica among employees can vary over time. In 2011, Fevotte et al. (Févotte et al., 2011) used the Matgéné JEM to estimate that the whole-career prevalence of exposure to crystalline silica dust in a population of men aged 25 to 74 was 15.6% (95% CI: 14.6, 16.5%) in France in 2007 – a value very similar to those found here. Lastly, our high prevalence might indicate that exposure is more frequent in northern France than in the country as a whole, particularly in Dunkirk which is a highly industrialised city area. To the best of our knowledge, French regional data on exposure to silica are not available, and French national data are scarce (apart from the SUMER survey). Internationally, there are few studies of the prevalence of silica exposure in the general population; most of the published studies evaluated populations working in highly exposed sectors (Si et al., 2016). In its 2011 "Socioeconomic, Health and Environment and Cancer at Work" report, the Institute of Occupational Medicine estimated that about 5,300,000 workers in the European Union (i.e. around 2.6% of the active population) were potentially exposed to silica in 2006 (Institute of Occupational Medicine, 2011). Outside the European continent, Si et al. estimated that 6.6% (95% CI: 4.1, 9.5%) of the active population in Australia had been exposed to crystalline silica dust in 2012 (Si et al., 2016). Peters et al. estimated that the prevalence in Canada was 2.3% in 2006 (Peters et al., 2015). Again, it must be borne in mind that these are not whole-career prevalence values, which might explain (at least in part) the differences with our estimates.

We only included men in the present study because the proportion of female participants exposed to crystalline silica dust was extremely low (10 out of 1603, i.e. 0,6%). This low prevalence didn't allow stratification or adjustment on sex. We couldn't study exposure to crystalline silica in women. It should be noted that according to the SUMER survey, the estimated proportion of female employees exposed to silica in France in 2017 was 0.2% (Matinet et al., 2020).

4.2. FEV_1/FVC and CEI_{silica}

In our study, the FEV_1/FVC z-score decreased significantly with an increment in CEI_{silica} (after adjustment). In 2014, Brüske et al.'s systematic review of the literature (covering 10 studies) and meta-analysis (covering six) evaluated quantitative data on exposure to silica-containing dust from direct measurements or from an JEM (Brüske et al., 2014). The researchers observed a significant association between a low FEV_1/FVC ratio and cumulative occupational exposure to crystalline silica dust. In this meta-analysis, only one study (that performed by Meijer et al.) expressed the spirometry results as z-scores (calculated from predicted values published by the European Steel and Coal Community in 1993 (ECSC-93) (Quanjer et al., 1993)). Meijer et al. also evidenced a negative association between the FEV_1/FVC z-score and exposure to silica. More recently, Hoet et al., 's 2017 literature review (Hoet et al., 2017) sought to determine whether the current OELs (set to limit the likelihood of developing silicosis) were appropriate for avoiding the development of AOs and included the same studies as Brüske et al. (2014)

Table 3
Association between the FEV1/FVC or FEF25-75 z-scores with the CEIsilica (in mg.m-3.year) and the CEIs for vapours, gases, fumes, and dusts (other than silica dust).

	FEV_1/FVC z-score (*n* = *1428*)			FEF_{25-75} z-score (*n* = *1414*)		
	Model 0	Model 1	Model 2	Model 0	Model 1	Model 2
	Beta (95%CI)	Beta (95%CI)	Beta (95%CI)	Beta (95%CI)	Beta (95%CI)	Beta (95%CI)
CEI silica ($mg.m^{-3}$. year)	−0.114 (−0.223, −0.005)	−0.112 (−0.216, −0.007)	−0.133 (−0.242, −0.024)	−0.154 (−0.271, −0.037)	−0.142 (−0.253, −0.031)	−0.162 (−0.278, −0.046)
CEI vapours (u.year)	−0.001 (−0.003, 0.001)	–	−0.0004 (−0.004, 0.003)	−0.002 (−0.004, 0.0002)	–	−0.001 (−0.005, 0.002)
CEI gases (u.year)	−0.001 (−0.003, 0.001)	–	0.001 (−0.003, 0.004)	−0.001 (−0.003, 0.001)	–	0.001 (−0.003, 0.004)
CEI fumes (u.year)	−0.001 (−0.002, 0.001)	–	0.001 (−0.003, 0.004)	−0.002 (−0.003, 0.0002)	–	0.001 (−0.003, 0.004)
CEI dusts[a] (u.year)	−0.002 (−0.004, 0.0001)	–	−0.003 (−0.005, −0.001)	−0.003 (−0.005, −0.001)	–	−0.003 (−0.005, −0.001)

Note: FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; FEF_{25-75}: mean forced expiratory flow between 25% and 75% of the FVC; CI: confidence interval; CEI_{silica}: Cumulative exposure index for crystalline silica dust; CEI: cumulative exposure index. Model 0: non-adjusted. Model 1: adjusted for age, body mass index, tobacco use status, city area, history of asthma, and season. Model 2: model 1 adjusted for the CEIs for vapours, gases, fumes, and dusts (other than silica).
[a] Dusts other than silica.

Table 4
Association between the FEV1/FVC or FEF25-75 z-scores and the CEIsilica in three classes (non-exposed, exposed above and below a 1 mg.m-3.year threshold).

CEI_{silica}	FEV_1/FVC z-score (*n* = *1428*)				FEF_{25-75} z-score (*n* = *1414*)			
	n	Model 0	Model 1	Model 2	n	Model 0	Model 1	Model 2
		Beta (95%CI)	Beta (95%CI)	Beta (95%CI)		Beta (95%CI)	Beta (95%CI)	Beta (95%CI)
Non-exposed	1135	ref.	ref.	ref.	1124	ref.	ref.	ref.
<1 $mg\ m^{-3}$. year	262	−0.042 (−0.178, 0.095)	−0.071 (−0.204, 0.062)	−0.152 (−0.309, 0.005)	260	−0.088 (−0.235, 0.058)	−0.107 (−0.249, 0.034)	−0.191 (−0.358, −0.025)
≥1 $mg\ m^{-3}$. year	31	−0.338 (−0.702, 0.025)	−0.311 (−0.660, 0.038)	−0.426 (−0.792, −0.060)	30	−0.484 (−0.879, −0.089)	−0.424 (−0.800, −0.048)	−0.552 (−0.947, −0.157)

Note: FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; FEF_{25-75}: forced expiratory flow between 25% and 75% of the FVC; CI: confidence interval; CEI_{silica}: Cumulative exposure index for crystalline silica dust. Model 0: non-adjusted. Model 1: adjusted for age, body mass index, tobacco use status, city area, history of asthma, and season. Model 2: model 1 adjusted for the CEIs for vapours, gases, fumes, and dusts (other than silica).

Table 5
Associations between the presence of AO or an impaired FEF25-75 with the CEIsilica (in mg.m-3.year) or the CEIs for vapours, gases, fumes, dusts (other than silica).

	AO (*n* = *1428*)			Impaired FEF_{25-75} (*n* = *1414*)		
	Model 0	Model 1	Model 2	Model 0	Model 1	Model 2
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
CEI silica ($mg.m^{-3}$.year)	1.188 (0.898, 1.513)	1.202 (0.904, 1.562)	1.285 (0.96, 1.716)	1.281 (0.96, 1.652)	1.299 (0.96, 1.725)	1.343 (0.98, 1.834)
CEI vapours (u.year)	1.001 (0.99, 1.007)	–	0.999 (0.99, 1.009)	1.003 (0.995, 1.009)	–	1.004 (0.99, 1.015)
CEI gases (u.year)	1.002 (0.996, 1.007)	–	1.003 (0.99, 1.015)	1.002 (0.996, 1.008)	–	1.000 (0.99, 1.014)
CEI fumes (u.year)	1.000 (0.995, 1.005)	–	0.990 (0.98, 1.004)	1.002 (0.996, 1.008)	–	0.997 (0.98, 1.009)
CEI dusts[a] (u.year)	1.004 (0.999, 1.009)	–	1.008 (1.001, 1.015)	1.004 (0.998, 1.010)	–	1.006 (0.998, 1.014)

Note: AO: airway obstruction (defined as a GLI-2012 z-score for the FEV_1/FVC ratio < −1.645); FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; FEF_{25-75}: forced expiratory flow between 25 and 75% of the FVC (impairment was defined as a GLI-2012 z-score < −1.645); OR: odds ratio; CI: confidence interval; CEI_{silica}: Cumulative exposure index for crystalline silica dust; CEI: cumulative exposure index. Model 0: non-adjusted. Model 1: adjusted for age, body mass index, tobacco use status, city area, history of asthma, and season. Model 2: model 1 adjusted for the CEIs for vapours, gases, fumes, and dusts (other than silica).
[a] Dusts other than silica.

Furthermore, we did not observe a significant association between the presence of AO and the value of CEI_{silica} in $mg.m^{-3}$.year. This lack of an association might be due to the loss of statistical power that results from moving from a continuous value (the FEV_1/FVC z-score) to a categorical (binary) value (i.e. the presence or absence of AO) in the model. There are few literature data on the risk of developing AO as a function of quantitative exposure to silica dust. Most of the studies using absolute values, % predicted values or z-scores, rather than a binary criterion (the presence or absence of AO). Hoet et al.'s literature review (Hoet et al., 2017) included only one nested case-control study (by Möhner et al.), which evidenced an increase in the likelihood of GOLD stage I COPD (Global initiative for chronic obstructive lung disease, 2022) for a 1 mg m^{-3}.year increment in the CEI_{silica} in uranium miners (OR: 1.81 (95% CI: 1.27, 2.56) after adjustment for tobacco use). (Möhner et al., 2012).

4.3. FEV_1/FVC and the CEI_{silica} threshold of 1 mg m^{-3}.year

Although the link between AOs and silica dust exposure has been well established qualitatively, Hoet et al.'s systematic review of the literature (Hoet et al., 2017) concluded that there is not currently enough evidence of a dose-response relationship with a threshold for exposure to crystalline silica. We chose to test a 1 mg m^{-3}.year threshold because it is defined as a high level of exposure in the HAS guidelines (Hulo et al., 2021). Thus, relative to non-exposed participants, participants with a CEI_{silica} ≥1 mg m^{-3}.year had a significantly lower FEV_1/FVC z-score and a significantly higher likelihood of presenting AO.

Table 6
Association between the presence of AO or an impaired FEF25-75 value with the CEIsilica in three classes (non-exposed, exposed above or below a 1 mg.m-3.year threshold).

CEI_{silica}	AO (*n* = *1428*)				Impaired FEF_{25-75} (*n* = *1414*)			
	n	Model 0	Model 1	Model 2	n	Model 0	Model 1	Model 2
		OR (95%CI)	OR (95%CI)	OR (95%CI)		OR (95%CI)	OR (95%CI)	OR (95%CI)
Non-exposed	1135	ref.	ref.	ref.	1124	ref.	ref.	ref.
<1 mg m^{-3}.year	262	1.014 (0.662, 1.510)	1.052 (0.676, 1.597)	1.357 (0.825, 2.179)	260	1.032 (0.606, 1.680)	1.165 (0.668, 1.952)	1.366 (0.734, 2.441)
≥1 mg m^{-3}.year	31	2.125 (0.832, 4.781)	2.103 (0.800, 4.911)	3.056 (1.107, 7.626)	30	3.095 (1.122, 7.325)	3.237 (1.128, 8.064)	4.305 (1.393, 11.79)

Note: AO: airway obstruction (defined as a GLI-2012 z-score for the FEV_1/FVC ratio < −1.645); FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; FEF_{25-75}: forced expiratory flow between 25 and 75% of the FVC (impairment was defined as a GLI-2012 z-score < −1.645); OR: odds ratio; CI: confidence interval; CEI_{silica}: Cumulative exposure index for crystalline silica dust. Model 0: non-adjusted. Model 1: adjusted for age, body mass index, tobacco use status, city area, history of asthma, and season. Model 2: model 1 adjusted for the CEIs for vapours, gases, fumes, and dusts (other than silica).

This latter aspects clearly indicated that a threshold of 1 mg m^{-3}.year is clinically relevant and can serve as a guide for monitoring exposed workers. In 2020, Mönher et al. suggested that a threshold of about 2 mg m^{-3}.year should be used as a criterion for diagnosing occupational COPD (Möhner and Nowak, 2020). Like us, Mönher et al. assessed GLI-2012 z-scores but used spirometry data collected between 1971 and 1990 among uranium miners below the age of 37. This selection of a population of young workers (some researchers consider that COPD onset before the age of 50 years is early (Martinez et al., 2018; Soriano et al., 2018)) with high occupational exposure doubtless led to the calculation of an overly restrictive threshold, relative to a value of 1 mg m^{-3}.year. Indeed, our analysis of a population of older individuals (some of whom were no longer in work) avoided bias due to a “healthy worker” effect and highlighted an effect of levels above 1 mg m^{-3}.year.

4.4. *FEF_{25-75}*

In our study, the FEF_{25-75} z-score fell significantly as the CEI_{silica} increased, and the likelihood of presenting an impaired FEF_{25-75} was significantly greater when the CEI_{silica} exceeded 1 mg m^{-3}.year. A low FEF_{25-75} value reflects the obstruction of small airways (defined as those with an internal diameter ≤2 mm), which makes a non-negligeable contribution to the resistance to ventilatory flow seen in obstructive diseases (Macklem, 1998; Stockley et al., 2017a). Although other spirometry parameters (such as the instantaneous forced expiratory flow when 25% (FEF25) or 75% (FEF75) of the FVC has been expired) can be used to study the small airways, the FEF_{25-75} is still the most widely used and the most thoroughly characterized (Stockley et al., 2017a). Taking account of small airway obstruction (notably through the use of spirometry indices like FEF_{25-75}) is sometimes criticised in the literature because these indices supposedly do not provide more information than the FEV_1 and the FEV_1/FVC ratio (Quanjer et al., 2014). This hypothesis is subject to debate, and some researchers have emphasized the importance of taking small airway obstruction into account (Havet et al., 2020; Papi et al., 2020; Stockley et al., 2017a; Xiao et al., 2020). In fact, damage to these airways might precede an impairment in FEV_1 or the appearance of emphysema in patients with early-stage COPD (Hogg et al., 2004; McDonough et al., 2011; Stockley et al., 2017b). Usmani et al., ‘s 2021 literature review came to the same conclusions (Usmani et al., 2021). All these literature data suggest that monitoring the decline in FEF_{25-75} is of significant value in early health screening for obstructive pathologies - notably in an occupational exposure setting. Early screening might enable better monitoring during the career and, above all, after retirement, when more severe obstructive pathologies can appear. Another often-cited argument against the use of FEF_{25-75} is its supposedly high variability (Garcia et al., 2012). We mitigated this shortcoming by systematically and rigorously checking the acceptability of the flow-volume curves; this was always done by the same specialist and complied with the standardized 2005 ATS/ERS guidelines (Miller et al., 2005). Moreover, we observed a significant decrement in the FEF_{25-75} z-score as the CEI_{silica} in mg.m^{-3}.year increased, after adjustment for occupational exposure in participants with a normal FVC (Stockley et al., 2017a). To the best of our knowledge, few studies have evaluated the relationship between exposure to crystalline silica dust and an impairment in FEF_{25-75} in particular or small airway obstruction in general. In 2020, Ulvestad et al. found results similar to ours, namely, that the cumulative respirable crystalline silica exposure was significantly associated with the decreased of the FEF_{25-75} (in % predicted calculated using the ECSC-93 equations) in 136 Norwegian male rock drillers, after adjustment for the smoking status and asthma only (Ulvestad et al., 2020). In 2000, Koo et al. found that the mean FEF_{25-75} (in % predicted) was significantly lower in Korean people exposed to silica than in their non-exposed counterparts (66.7 ± 22.2% and 93.4 ± 13.8%, respectively, vs. 98.8 ± 35.2% and 103 ± 36.4% for the exposed and non-exposed groups in our study). However, Koo et al. did not adjust their figures for other variables (such as tobacco use), and all their participants were in work at the time of the study (Koo et al., 2000). In a 2001 study of 144 exposed employees and 110 non-exposed employees, Meijer et al. did not find a significant association between exposure to concrete dust (which contains a high proportion of silica) and FEF_{25-75} after adjustment for tobacco use and a history of respiratory allergy, regardless of whether exposure was handled as a binary variable or quantified by measurement in the workplace (Meijer et al., 2001). Lastly, in 1994, Neukrich et al. showed that FEF_{25-75} values were significantly lower in people exposed to silica after adjustment for age, height, and tobacco use (men and women were analyzed separately) (Neukirch et al., 1994). Neukrich et al. did not measure or quantitatively estimate exposure. In fact, most studies considered a binary variable (exposed/non-exposed) or measurements of exposure performed in the workplace at the time of the study. Furthermore, none of the studies in the literature applied the GLI-2012 standards to the FEF_{25-75} measurements.

4.5. *Strengths and limitations*

Our study had some limitations. In the interview, each participant was asked about his first job, his latest job, the job that he had done for the longest during his career, and the various jobs that might have led to exposure to vapours, gases, fumes and/or dusts. Hence, potential occupational exposure was not recorded exhaustively, and so exposure might have been underestimated for some of the participants. Furthermore, we did not take account of possible silicosis, which can also lead to AO and for which the dose-effect relationship is well established (Anses, 2019). However, some researchers have criticized attempts to include silicosis in the models. Bruske et al. (Brüske et al., 2014) pointed out that taking account of silicosis partly attenuates the effect of the exposure in the most exposed individuals; this justified the non-inclusion in their meta-analysis of a study in which a multiple linear regression model was adjusted for silicosis. In most of the studies of the relationship between AO and silica exposure, the latter was measured directly in the workplace (Brüske et al., 2014; Hoet et al., 2017); in contrast, we used a JEM. Direct measurements are advantageous in that they accurately reflect exposure in the individual's current workplace. In contrast, direct measurements do not take account of possible exposure in previous jobs or in the same job but under different conditions (i.e. with different personal or collective protective equipment, for example). A JEM takes account of previous exposure and changes in the intensity of the exposure over time; for example, exposure protection and the regulations for a given profession were not the same in 1970 and in 2000. It should be noted, however, that the JEM does not take into account the tasks performed within the job, but only the job as a whole, which may lead to classification errors. Nevertheless, the JEM remains an essential method in a general population epidemiological study with such a large number of subjects, it is indeed very difficult to take into account all the tasks for all the occupations over the entire career. It is also worth noticing that even if we found significant association between ventilatory disorders and exposure to silica of at least 1 mg m^{-3}.year, those results were obtained on a small number of subject and should be interpreted carefully. Lastly, we did not perform reversibility tests during the spirometry measurements, and so reversible AOs cannot be ruled out. We tried to mitigate this bias by taking account of the history of asthma in the analyses; for isolated asthma, one would expect the AO to be reversible. However, as pointed out by Hoet et al. reversibility tests are very rarely performed during occupational health monitoring (Hoet et al., 2017), and so our procedures were quite similar to those used in real life.

Our study also had several strengths. Firstly, it was performed in the general population, which avoided bias from a "healthy worker" effect (Eisen et al., 1995). Thus, we were able to include not only currently or previously exposed individuals in work but also previously exposed individuals who had retired or were no longer in work (e.g. for health reasons). Of the six studies in Brüske et al.'s meta-analysis, only one included retired individuals (Brüske et al., 2014). Our study design also enabled us to estimate the prevalence of the exposure to silica in the general population. Almost all of the literature data come from case-control surveys in which exposed employees are matched with non-exposed employees. For example, the proportion of exposed individuals in Brüske et al.'s meta-analysis ranged from 24% to 57% (Brüske et al., 2014). Furthermore, it is noteworthy that the acceptability of the flow-volume curves was checked (by the same specialist, in all cases) against the ATS/ERS-2005 guidelines (Miller et al., 2005); this was not the case in all the other studies (Hoet et al., 2017) and helped to attenuate the often-reported variability in the FEF_{25-75} data (Garcia et al., 2012). Furthermore, we calculated the predicted spirometry values by using the GLI-2012 equations (Quanjer et al., 2012); this is novel because most of the previous research was performed before these equations were published (Hoet et al., 2017). To the best of our knowledge, only Mönher et al. have used GLI-2012 equations in this context (Möhner and Nowak, 2020). The GLI-2012 standards have already been validated for use in the general population in France (Hulo et al., 2016). Our analyses also took account of other exposures (vapours, gases, fumes and dusts), which is rarely the case in the literature (Hoet et al., 2017), that might be co-exposures and for which several studies have shown relationships with respiratory disorders (from reduced ventilatory function to chronic obstructive pulmonary disease) (Omland et al., 2014; Tagiyeva et al., 2017; Vinnikov et al., 2019). Not taking these co-exposures into account (model 1) may be more relevant when estimating a risk related to a global exposure, as workers exposed to silica have multiple exposures. However, to study the specific effect of silica exposure, the models including the exposures to vapours, gases, fumes and dusts (model 2) is more relevant because in model 1, the effect could be explained by co-exposures and not by silica alone. The model 1 may underestimate the risk related to workers' co-exposures. Lastly, we used the Matgéné JEM (the methodology for which has been published) to calculate the CEI_{silica} (Févotte et al., 2011).

5. Conclusion

We evidenced a significant impact of exposure to crystalline silica dust on respiratory function (bronchial obstruction and small airway obstruction). An impaired FEV_1/FVC and an impaired FEF_{25-75} became more frequent as the CEI_{silica} - particularly among participants exposed to 1 mg m^{-3}.year or more. Our results emphasize the likely importance of spirometry-based monitoring among individuals at or above the silica exposure threshold of 1 mg m^{-3}.year.

Credit author statement

PM Wardyn: Conceptualization, Methodology, Formal analysis, Writing – original draft; JL Edme: Conceptualization, Methodology, Writing – review & editing; V de Broucker: Writing – review & editing; N Cherot-Kornobis: Writing – review & editing; D Ringeval: Methodology, Writing – review & editing; P Amouyel: Funding acquisition, Conceptualization, Writing – review & editing; A Sobaszek: Writing – review & editing; L. Dauchet: Investigation, Funding acquisition, Conceptualization, Writing – review & editing, Project administration; S Hulo: Supervision, Conceptualization, Methodology, Writing – original draft.

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Ethical aspects

The study protocol was registered at ClinicalTrials.gov (identifier: NCT02490553) and had been approved by the local independent ethics committee (CPP Nord Ouest IV, Lille, France; reference: 2010-A00065-34), in compliance with the French legislation on biomedical research. All the participants gave their written, informed consent prior to inclusion in the study.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.115382.

References

Anses, 2019. Mise à jour des connaissances concernant les dangers, expositions et risques relatifs à la silice cristalline. Saisine n°2015-SA-0236 - Silice cristalline (Avis). Anses, Maisons-Alfort, Île de France, France.

Brüske, I., Thiering, E., Heinrich, J., Huster, K.M., Nowak, D., 2014. Respirable quartz dust exposure and airway obstruction: a systematic review and meta-analysis. Occup. Environ. Med. 71, 583–589. https://doi.org/10.1136/oemed-2013-101796.

Chérot-Kornobis, N., Hulo, S., Giovannelli, J., de Broucker, V., Matran, R., Amouyel, P., Sobaszek, A., Dauchet, L., Edmé, J.-L., 2018. Exhaled breath NOx levels in a middle-aged adults population-based study: reference values and association with the smoking status. Respir. Med. 137, 134–140. https://doi.org/10.1016/j.rmed.2018.03.002.

Clement, G., Giovannelli, J., Cottel, D., Montaye, M., Ciuchete, A., Dallongeville, J., Amouyel, P., Dauchet, L., 2017. Changes over time in the prevalence and treatment of cardiovascular risk factors, and contributions to time trends in coronary mortality over 25 years in the Lille urban area (northern France). Archives of Cardiovascular Diseases 110, 689–699. https://doi.org/10.1016/j.acvd.2017.03.009.

Dauchet, L., Hulo, S., Cherot-Kornobis, N., Matran, R., Amouyel, P., Edmé, J.-L., Giovannelli, J., 2018. Short-term exposure to air pollution: Associations with lung function and inflammatory markers in non-smoking, healthy adults. Environ. Int. 121, 610–619. https://doi.org/10.1016/j.envint.2018.09.036.

Delabre, L., Pilorget, C., Garras, L., Févotte, J., 2010. Groupe de travail Matgéné, 2010. Éléments techniques sur l'exposition professionnelle aux poussières alvéolaires de silice cristalline libre. Présentation d'une matrice emplois-expositions aux poussières alvéolaires de silice cristalline libre.

Devien, L., Giovannelli, J., Cuny, D., Matran, R., Amouyel, P., Hulo, S., Edmé, J.L., Dauchet, L., 2018. Sources of household air pollution: the association with lung function and respiratory symptoms in middle-aged adult. Environ. Res. 164, 140–148. https://doi.org/10.1016/j.envres.2018.02.016.

Eisen, E.A., Wegman, D.H., Louis, T.A., Smith, T.J., Peters, J.M., 1995. Healthy worker effect in a longitudinal study of one-second forced expiratory volume (FEV1) and chronic exposure to granite dust. Int. J. Epidemiol. 24, 1154–1162. https://doi.org/10.1093/ije/24.6.1154.

Févotte, J., Dananché, B., Delabre, L., Ducamp, S., Garras, L., Houot, M., Luce, D., Orlowski, E., Pilorget, C., Lacourt, A., Brochard, P., Goldberg, M., Imbernon, E., 2011. Matgéné: a program to develop job-exposure matrices in the general population in France. Ann. Occup. Hyg. 55, 865–878. https://doi.org/10.1093/annhyg/mer067.

Garcia, G., Perez, T., Verbanck, S., 2012. Explorations fonctionnelles respiratoires des voies aériennes distales dans la BPCO. Rev. Mal. Respir. 29, 319–327. https://doi.org/10.1016/j.rmr.2011.09.042.

Giovannelli, J., Trouiller, P., Hulo, S., Chérot-Kornobis, N., Ciuchete, A., Edmé, J.-L., Matran, R., Amouyel, P., Meirhaeghe, A., Dauchet, L., 2018. Low-grade systemic inflammation: a partial mediator of the relationship between diabetes and lung function. Ann. Epidemiol. 28, 26–32. https://doi.org/10.1016/j.annepidem.2017.11.004.

Global initiative for chronic obstructive lung disease, 2022. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [WWW Document]. URL. https://goldcopd.org/wp-content/uploads/2021/12/GOLD-REPORT-2022-v1.1-22Nov2021_WMV.pdf. accessed 12.2.22.

Groupe de travail Matgéné, 2010. Présentation d'une matrice emplois-expositions aux poussières alvéolaires de silice cristalline libre – Quelques applications à un échantillon de population en France.

Havet, A., Hulo, S., Cuny, D., Riant, M., Occelli, F., Cherot-Kornobis, N., Giovannelli, J., Matran, R., Amouyel, P., Edmé, J.-L., Dauchet, L., 2020. Residential exposure to outdoor air pollution and adult lung function, with focus on small airway obstruction. Environ. Res. 183, 109161 https://doi.org/10.1016/j.envres.2020.109161.

Hoet, P., Desvallées, L., Lison, D., 2017. Do current OELs for silica protect from obstructive lung impairment? A critical review of epidemiological data. Crit. Rev. Toxicol. 47, 655–682. https://doi.org/10.1080/10408444.2017.1315363.

Hogg, J.C., Chu, F., Utokaparch, S., Woods, R., Elliott, W.M., Buzatu, L., Cherniack, R.M., Rogers, R.M., Sciurba, F.C., Coxson, H.O., Paré, P.D., 2004. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N. Engl. J. Med. 350, 2645–2653. https://doi.org/10.1056/NEJMoa032158.

Hulo, S., Broucker, V. de, Giovannelli, J., Cherot-Kornobis, N., Nève, V., Sobaszek, A., Dauchet, L., Edmé, J.-L., 2016. Global Lung Function Initiative reference equations better describe a middle-aged, healthy French population than the European Community for Steel and Coal values. Eur. Respir. J. 48, 1779–1781. https://doi.org/10.1183/13993003.00606-2016.

Hulo, S., Pairon, J.-C., Brochard, P., Autorité de Santé, Haute, 2021. Surveillance médico-professionnelle des travailleurs exposés ou ayant été exposés à la silice cristalline. Recommandation de bonne pratique labellisée par la Haute Autorité de santé (Recommandation de bonne pratique). Haute Autorité de Santé, France.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2012. Arsenic, metals, fibres, and dusts. IARC Monogr. Eval. Carcinog. Risks Hum. 100, 11–465.

Institut national de la statistique et des études économiques, 2008. Nomenclature d'activités française – NAF rév. 2 [WWW Document]. Insee. URL. https://www.insee.fr/fr/information/2120875. accessed 12.2.22.

Institut national de la statistique et des études économiques, 2003. Professions et catégories socioprofessionnelles - PCS 2003 [WWW Document]. Insee. URL. https://www.insee.fr/fr/information/2400059. accessed 12.2.22.

Institute of Occupational Medicine, 2011. Health, socio-economic and environmental aspects of possible amendments to the EU Directive on the protection of workers from the risks related to exposure to carcinogens and mutagens at work. In: IOM Research Project, P937/99. Institute of Occupational Medicine, Ricarton, Edinburgh, United Kingdom.

Koo, J.W., Chung, C.K., Park, C.Y., Lee, S.-H., Lee, K.-S., Roh, Y.-M., Yim, H.W., 2000. The effect of silica dust on ventilatory function of foundry workers. J. Occup. Health 42, 251–257. https://doi.org/10.1539/joh.42.251.

Leung, C.C., Yu, I.T.S., Chen, W., 2012. Silicosis. Lancet 379, 2008–2018. https://doi.org/10.1016/S0140-6736(12)60235-9.

Macklem, P.T., 1998. The physiology of small airways. Am. J. Respir. Crit. Care Med. 157, S181–S183. https://doi.org/10.1164/ajrccm.157.5.rsaa-2.

Mahler, D.A., Wells, C.K., 1988. Evaluation of clinical methods for rating dyspnea. Chest 93, 580–586. https://doi.org/10.1378/chest.93.3.580.

Martinez, F.J., Han, M.K., Allinson, J.P., Barr, R.G., Boucher, R.C., Calverley, P.M.A., Celli, B.R., Christenson, S.A., Crystal, R.G., Fagerås, M., Freeman, C.M., Groenke, L., Hoffman, E.A., Kesimer, M., Kostikas, K., Paine, R., Rafii, S., Rennard, S.I., Segal, L. N., Shaykhiev, R., Stevenson, C., Tal-Singer, R., Vestbo, J., Woodruff, P.G., Curtis, J. L., Wedzicha, J.A., 2018. At the root: defining and halting progression of early chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. 197, 1540–1551. https://doi.org/10.1164/rccm.201710-2028PP.

Matinet, B., Rosankis, E., Léonard, M., 2020. Les expositions aux risques professionnels : les produits chimiques, Synthèse.Stat'. Dares. Île de France, Paris (France).

McDonough, J.E., Yuan, R., Suzuki, M., Seyednejad, N., Elliott, W.M., Sanchez, P.G., Wright, A.C., Gefter, W.B., Litzky, L., Coxson, H.O., Paré, P.D., Sin, D.D., Pierce, R.A., Woods, J.C., McWilliams, A.M., Mayo, J.R., Lam, S.C., Cooper, J.D., Hogg, J.C., 2011. Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. N. Engl. J. Med. 365, 1567–1575. https://doi.org/10.1056/NEJMoa1106955.

Meijer, E., Kromhout, H., Heederik, D., 2001. Respiratory effects of exposure to low levels of concrete dust containing crystalline silica. Am. J. Ind. Med. 40, 133–140. https://doi.org/10.1002/ajim.1080.

Miller, M.R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., Crapo, R., Enright, P., Grinten, C.P.M. van der, Gustafsson, P., Jensen, R., Johnson, D.C., MacIntyre, N., McKay, R., Navajas, D., Pedersen, O.F., Pellegrino, R., Viegi, G., Wanger, J., 2005. Standardisation of spirometry. Eur. Respir. J. 26, 319–338. https://doi.org/10.1183/09031936.05.00034805.

Möhner, M., Kersten, N., Gellissen, J., 2012. Chronic obstructive pulmonary disease and longitudinal changes in pulmonary function due to occupational exposure to respirable quartz. Occup. Environ. Med. 70, 9–14. https://doi.org/10.1136/oemed-2012-100775.

Möhner, M., Nowak, D., 2020. Estimation of an exposure threshold value for compensation of silica-induced COPD based on longitudinal changes in pulmonary function. Int. J. Environ. Res. Publ. Health 17, 9040. https://doi.org/10.3390/ijerph17239040.

Neukirch, F., Cooreman, J., Korobaeff, M., Pariente, R., 1994. Silica exposure and chronic airflow limitation in pottery workers. Arch. Environ. Health 49, 459–464. https://doi.org/10.1080/00039896.1994.9955001.

Omland, Ø., Würtz, E.T., Aasen, T.B., Blanc, P., Brisman, J.B., Miller, M.R., Pedersen, O. F., Schlünssen, V., Sigsgaard, T., Ulrik, C.S., Viskum, S., 2014. Occupational chronic obstructive pulmonary disease: a systematic literature review. Scand. J. Work. Environ. Health 40, 19–35. https://doi.org/10.5271/sjweh.3400.

OSHA, 2016. Occupational Exposure to Respirable Crystalline Silica. Occupational Safety and Health Administration., Washington, DC. Final Rule. 29 CFR Parts 1910, 1915, and 1926.

Papi, A., Morandi, L., Fabbri, L., 2020. Small airway dysfunction: not so silent after all? Lancet Respir. Med. 8, 1062–1063. https://doi.org/10.1016/S2213-2600(20)30169-7.

Peters, C.E., Ge, C.B., Hall, A.L., Davies, H.W., Demers, P.A., 2015. CAREX Canada: an enhanced model for assessing occupational carcinogen exposure. Occup. Environ. Med. 72, 64–71. https://doi.org/10.1136/oemed-2014-102286.

Polverino, F., Soriano, J.B., 2020. Small airways and early origins of COPD: pathobiological and epidemiological considerations. Eur. Respir. J. 55 https://doi.org/10.1183/13993003.02457-2019.

Quach, A., Giovannelli, J., Chérot-Kornobis, N., Ciuchete, A., Clément, G., Matran, R., Amouyel, P., Edmé, J.-L., Dauchet, L., 2015. Prevalence and underdiagnosis of airway obstruction among middle-aged adults in northern France: the ELISABET study 2011–2013. Respir. Med. 109, 1553–1561. https://doi.org/10.1016/j.rmed.2015.10.012.

Quanjer, P.H., Stanojevic, S., Cole, T.J., Baur, X., Hall, G.L., Culver, B.H., Enright, P.L., Hankinson, J.L., Ip, M.S.M., Zheng, J., Stocks, J., the ERS Global Lung Function Initiative, 2012. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur. Respir. J. 40, 1324–1343. https://doi.org/10.1183/09031936.00080312.

Quanjer, P.H., Tammeling, G.J., Cotes, J.E., Pedersen, O.F., Peslin, R., Yernault, J.-C., 1993. Lung volumes and forced ventilatory flows. Eur. Respir. J. 6, 5–40. https://doi.org/10.1183/09041950.005s1693.

Quanjer, P.H., Weiner, D.J., Pretto, J.J., Brazzale, D.J., Boros, P.W., 2014. Measurement of FEF25–75% and FEF75% does not contribute to clinical decision making. Eur. Respir. J. 43, 1051–1058. https://doi.org/10.1183/09031936.00128113.

R Core Team, 2013. R: A Language and Environment for Statistical Computing.

Riant, M., Meirhaeghe, A., Giovannelli, J., Occelli, F., Havet, A., Cuny, D., Amouyel, P., Dauchet, L., 2018. Associations between long-term exposure to air pollution, glycosylated hemoglobin, fasting blood glucose and diabetes mellitus in northern France. Environ. Int. 120, 121–129. https://doi.org/10.1016/j.envint.2018.07.034.

Si, S., Carey, R.N., Reid, A., Driscoll, T., Glass, D.C., Peters, S., Benke, G., Darcey, E., Fritschi, L., 2016. The Australian work exposures study: prevalence of occupational exposure to respirable crystalline silica. Ann. Occup. Hyg. 60, 631–637. https://doi.org/10.1093/annhyg/mew007.

Soriano, J.B., Polverino, F., Cosio, B.G., 2018. What is early COPD and why is it important? Eur. Respir. J. 52 https://doi.org/10.1183/13993003.01448-2018.

Stockley, J.A., Cooper, B.G., Stockley, R.A., Sapey, E., 2017a. Small airways disease: time for a revisit? COPD 12, 2343–2353. https://doi.org/10.2147/COPD.S138540.

Stockley, J.A., Ismail, A.M., Hughes, S.M., Edgar, R., Stockley, R.A., Sapey, E., 2017b. Maximal mid-expiratory flow detects early lung disease in α1-antitrypsin deficiency. Eur. Respir. J. 49 https://doi.org/10.1183/13993003.02055-2016.

Tagiyeva, N., Sadhra, S., Mohammed, N., Fielding, S., Devereux, G., Teo, E., Ayres, J., Graham Douglas, J., 2017. Occupational airborne exposure in relation to Chronic Obstructive Pulmonary Disease (COPD) and lung function in individuals without childhood wheezing illness: a 50-year cohort study. Environ. Res. 153, 126–134. https://doi.org/10.1016/j.envres.2016.11.018.

Ulvestad, B., Ulvestad, M., Skaugset, N.P., Aaløkken, T.M., Günther, A., Clemm, T., Lund, M.B., Ellingsen, D.G., 2020. Pulmonary function and high-resolution computed tomography in outdoor rock drillers exposed to crystalline silica. Occup. Environ. Med. 77, 611–616. https://doi.org/10.1136/oemed-2019-106254.

Usmani, O.S., Dhand, R., Lavorini, F., Price, D., 2021. Why we should target small airways disease in our management of chronic obstructive pulmonary disease. Mayo Clin. Proc. 96, 2448–2463. https://doi.org/10.1016/j.mayocp.2021.03.016.

Vinnikov, D., Raushanova, A., Kyzayeva, A., Romanova, Z., Tulekov, Z., Kenessary, D., Auyezova, A., 2019. Lifetime occupational history, respiratory symptoms and chronic obstructive pulmonary disease: results from a population-based study. Int. J. Chronic Obstr. Pulm. Dis. 14, 3025–3034. https://doi.org/10.2147/COPD.S229119.

Xiao, D., Chen, Z., Wu, S., Huang, Kewu, Xu, J., Yang, L., Xu, Y., Zhang, Xiangyan, Bai, Chunxue, Kang, J., Ran, P., Shen, H., Wen, F., Yao, W., Sun, T., Shan, G., Yang, T., Lin, Y., Zhu, J., Wang, R., Shi, Z., Zhao, J., Ye, X., Song, Y., Wang, Q., Hou, G., Zhou, Y., Li, W., Ding, L., Wang, H., Chen, Y., Guo, Y., Xiao, F., Lu, Y., Peng, X., Zhang, B., Wang, Z., Zhang, H., Bu, X., Zhang, Xiaolei, An, L., Zhang, S., Cao, Z., Zhan, Q., Yang, Y., Liang, L., Liu, Z., Zhang, Xinran, Cheng, A., Cao, B., Dai, H., Chung, K.F., He, J., Wang, Chen, Wang, Chen, He, J., Xu, J., Yang, L., Xu, Y., Zhang, Xiangyan, Bai, Chenxue, Kang, J., Ran, P., Shen, H., Wen, F., Huang, Kewu, Yao, W., Shan, G., Yang, T., Lin, Y., Wu, S., Zhu, J., Wang, R., Shi, Z., Zhao, J., Ye, X., Song, Y., Yang, D., Wang, Q., Hou, G., Zhou, Y., Li, W., Ding, L., Wan, C., Yang, T., Wang, H., Chen, Y., Guo, Y., Xiao, F., Lu, Y., Peng, X., Zhang, B., Xiao, D., Wang, Z., Bu, X., Zhang, H., Zhang, Xiaolei, An, L., Zhang, S., Cao, Z., Zhan, Q., Yang, Y., Cao, B., Dai, H., Liang, L., Wang, Chaolong, Tong, X., Wu, T., Kan, H., Chen, R., Cai, H., Xiong, W., Zhang, P., Li, Y., Niu, W., Chen, C.-S., Xu, G., Zhang, Xinran, Gu, X., Dong, F., Liu, Z., Cheng, A., Pei, Z., Niu, H., Huang, Ke, Chen, S., Chung, K.F., Chen, Z., 2020. Prevalence and risk factors of small airway dysfunction, and association with smoking, in China: findings from a national cross-sectional study. Lancet Respir. Med. 8, 1081–1093. https://doi.org/10.1016/S2213-2600(20)30155-7.