Prevalence of small airway dysfunction in the Swiss PneumoLaus Cohort

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Shareable abstract (@ERSpublications)
Prevalence of small airway dysfunction (SAD) was ⩽12.7% in an area with low air pollution levels. A low prevalence of SAD was associated with lower $PM_{2.5}$ exposure. MMEF <65% pred criterion carries a risk of overdiagnosing SAD in elderly individuals. https://bit.ly/3pDQTuJ

Cite this article as: Touilloux B, Bongard C, Lechartier B, *et al*. Prevalence of small airway dysfunction in the Swiss PneumoLaus Cohort. *ERJ Open Res* 2023; 9: 00381-2023 [DOI: 10.1183/23120541.00381-2023].

Received: 9 June 2023
Accepted: 3 July 2023

Abstract

Background Recent evidence identified exposure to particulate matter of size ⩽2.5 µm ($PM_{2.5}$) as a risk factor for high prevalence of small airway dysfunction (SAD). We assessed the prevalence of SAD in a European region with low air pollution levels.

Methods SAD was defined as a maximum mid-expiratory flow (MMEF) <65% of predicted value (PV) or MMEF <lower limit of normal (LLN) measured by spirometry in the Swiss PneumoLaus cohort. We performed bivariate and multivariable analysis with MMEF criteria, age, sex, body mass index, respiratory symptoms and smoking status. Mean $PM_{2.5}$ values were obtained from a Swiss national database.

Results Among 3351 participants (97.6% Caucasian, 55.7% female sex, mean age 62.7 years), we observed MMEF <65% PV in 425 (12.7%) and MMEF <LLN in 167 (5.0%) individuals. None of the participants had both MMEF <LLN and ⩾65% PV. MMEF <65% PV and MMEF <LLN were significantly associated with age, smoking status, cough, sputum and dyspnoea, whereas a positive association with MMEF <65% PV was observed for individuals aged >65 years only. In an area where ambient $PM_{2.5}$ concentration was <15 $\mu g \cdot m^{-3}$ during the observation period (2010 and 2020), ⩾72% of participants with SAD were ever-smokers.

Conclusions The observed low prevalence of SAD of 5.0–12.7% depending on criteria employed may be related to lower $PM_{2.5}$ exposure. Smoking was the main factor associated with SAD in an area with low $PM_{2.5}$ exposure. Employing a MMEF threshold <65% PV carries a risk of SAD overdiagnosis in elderly individuals.

Introduction

Early changes associated with airway diseases are thought to occur in small and distal airways. Therefore, there has been increasing interest in recent years to employ spirometry for assessment of small airway dysfunction (SAD) and treatment of preclinical obstructive lung disease with inhaled therapies containing newer generation extrafine particle formulations [1–4].

Despite this interest, larger population studies on the prevalence and risk factors of SAD are lacking [5, 6]. The BOLD study recently reported a wide geographical variation in the prevalence of SAD, ranging from 5% to 34% [7], and a recent review described a prevalence of between 7.5% and 45.9% [6]. In addition, Brenner *et al*. [8] reported a SAD prevalence of 25% in patients with stable heart failure (n=585). In

contrast, population-based studies from Asia reported high rates of SAD. Xiao *et al*. [9] report a prevalence of 43.5% estimated out of a population of 53 546 individuals, and Kwon *et al*. [10] estimate the prevalence at 30% among 3624 participants.

Despite the wide availability of spirometry, there is currently no accepted gold standard to diagnose SAD [1, 6, 11]. Forced expiratory volume in 1 s (FEV_1) has a low sensitivity for the diagnosis of SAD [12, 13]. The maximal mid-expiratory flow (MMEF) is defined as the flow between 25% and 75% of the forced vital capacity (FVC) ($FEF_{25–75}$) measured by spirometry from the largest sum of FEV_1 and FVC and therefore depends on the validity of the FVC measurement [11, 14].

As early as the 1970s, the MMEF was utilised to assess SAD, especially in the presence of normal FEV_1 or FEV_1/FVC ratio [15]. The MMEF is the most widely utilised parameter in the literature to assess SAD [6]. The historical normal range for MMEF published in 1963 based on standardised residuals/z-scores is broad [16], while lower limit of normal (LLN) varies widely between different populations [17]. Although the normal percentage of predicted value (PV) of MMEF is still contentious, a PV below 60–65% with a concomitant MMEF <LLN is commonly employed to define SAD [8, 10]. The combination of at least two of the following parameters is also described in the literature to define SAD: MMEF <65% and/or FEF_{50} <65% and/or FEF_{75} <65% PV [9, 18]. Nevertheless, current guidelines recommend to avoid employing a fixed cut-off to define abnormalities [12] with a preference to utilise LLN for the definition of SAD [6]. The measurement of FEV_3/FVC or FEV_3/FEV_6 <LLN has also been employed to define SAD [7, 19].

Evidence on the utility of MMEF to diagnose preclinical obstructive lung disease is available for asthma [20, 21], COPD [10, 22], α-1 antitrypsin deficiency [23] and bronchiolitis obliterans following lung transplantation [24, 25]. MMEF has been proposed as a more sensitive parameter than FEV_1 for assessing lung function in asthma patients with otherwise normal spirometry values [20, 26], but the role of MMEF for the diagnosis of SAD in COPD patients is debated. The prevalence of SAD and associated risk factors are largely unknown, therefore limiting its potential value in early management of obstructive lung disorders. Recently, evidence published by Xiao *et al*. [9] identified exposure to particulate matter of size ⩽2.5 µm ($PM_{2.5}$) as a possible risk factor for the high prevalence of SAD, along with smoking and a body mass index (BMI) ⩾25 $kg \cdot m^{-2}$.

Multiple factors likely influence lung function differences in the global population, and we hypothesised a low prevalence of SAD in our population study compared to data stemming from areas with a higher degree of air pollution. The purpose of this study based on the Swiss PneumoLaus cohort was twofold: first, to assess prevalence of SAD in a European area with low air pollution levels; and second, to identify associated risk factors.

Methods

Setting and selection of participants

PneumoLaus is a sub-study of the CoLaus|PsyCoLaus study (www.colaus-psycolaus.ch), a prospective and ongoing population-based cohort investigating the prevalence and determinants of cardiovascular disease in Lausanne, Switzerland. The sampling procedure of the CoLaus|PsyCoLaus study was previously described [27, 28]. Briefly, 6733 subjects (age range 35–75 years, 54% women) were recruited from a random sample of the population of Lausanne between June 2003 and May 2006. The first CoLaus|PsyCoLaus follow-up took place between April 2009 and September 2012, and a second follow-up between May 2014 and April 2017. PneumoLaus-related investigations took place between June 2014 and August 2017. The local Ethics Commission approved the CoLaus|PsyCoLaus study (www.cer-vd.ch; project number PB_2018-00038, reference 239/09), and all participants provided written informed consent.

Spirometric manoeuvres and parameters

Pulmonary function tests (PFTs) were performed using a MasterScreen-PFT spirometer (Carefusion, Hoechberg, Germany), employing the Sentry Suite software (Version 2.17). Measures were repeated to achieve a reproducible spirometry result, until a maximum of eight attempts, or interrupted if the participant was unable to continue. Each manoeuvre was analysed by computer in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) standards published in 2005 [29]. The GLI-2012 reference values were used, adjusting for ethnicity [30]. If FEV_1/FVC or FVC were below LLN, spirometry was repeated 10–15 min after administration of 400 µg of salbutamol.

Normal spirometry was defined by baseline FEV_1/FVC ratio and FVC above LLN [31]. A spirometry manoeuvre was accepted if the following criteria were fulfilled: absence of artefacts, abrupt termination, glottis closure, cough, leaks or large back-extrapolated volume; and presence of a maximal continuous effort [32].

Obstructive impairment evaluation

We defined fixed airflow obstruction as a FEV_1/FVC ratio below LLN following bronchodilation (BD). Post-BD normalised spirometry was defined as the FEV_1/FVC ratio below LLN before BD and above LLN after BD using the best FVC [28]. The presence of an FVC below LLN before BD that normalised after BD was also classified as a post-BD normalised spirometry because we suspected air trapping [31]. SAD was defined by MMEF before BD <65% PV or MMEF <LLN utilising GLI-2012 references values [30].

Respiratory risk factors

A face-to-face structured interview by the respiratory practitioner on the day of spirometry assessed respiratory risk factors, respiratory symptoms and putative prior respiratory diagnoses. Smoking status was categorised as current, former or never-smoker. Exposure to second-hand tobacco smoke during childhood and adulthood, as well as exposure to other fumes or smokes, were also assessed. Respiratory symptoms such as cough, sputum production and breathlessness according to the modified Medical Research Council (mMRC) dyspnoea scale were documented. Self-reported history and comorbidities were also recorded and previously described [28]. Healthy nonsmokers (HNS) were defined as subjects having never smoked, without cough, sputum, self-reported diagnosis of asthma, COPD or other lung disorders.

Data of annual mean ambient $PM_{2.5}$ and particulate matter size ⩽10 µm (PM_{10}) concentrations between 2010 and 2020 in Switzerland and regionally in Lausanne were extracted from the Swiss Federal Office for the Environment (FOEN) national open database and the Environmental Office from Vaud Country [33, 34].

Statistical analyses

Participant characteristics were expressed as n (%) for categorical variables, and as mean±SD or 95% confidence interval (95% CI) for continuous variables. Between-group comparisons were performed utilising chi-square, t-test or logistic regression for dichotomous variables. Multivariable analysis was conducted using logistic regression, with MMEF <65% PV or MMEF <LLN as the dependent variable and clinically significant covariates as independent variables. MMEF ⩾65% PV or MMEF ⩾LLN was considered the reference, and results were expressed as odds ratio and 95% CI. Statistical significance was considered for a two-sided test with $p<0.05$, and we employed Stata™ software (version 17.0; StataCorp, College Station, TX, USA).

Results

Participant selection and clinical characteristics

The PneumoLaus study enrolled 3353 (68.7%) participants of CoLaus|PsyCoLaus, of which 3351 (68.6%) were included in the analysis. Two participants were excluded due to uninterpretable spirometry. Detailed functional data on the population have been previously described [28]. The mean±SD BMI was 26.4±4.7 $kg \cdot m^{-2}$, 1329 (39.7%) subjects had a normal BMI, 55 (1.6%) were underweight, 1346 (40.2%) were overweight, 603 (18.0%) were obese and 18 (0.5%) had an unknown BMI, according to the World Health Organization (WHO) classification [35]. There was a slight female preponderance (n=1845, 55.7%), most participants were Caucasian (n=3273, 97.7%) and the mean age was 62.7 years (range 45.5–87.1). Of the total participants, 1686 (50.3%) were ever-smokers (18.2% current smokers and 32.1% former smokers) and 1498 (44.7%) healthy nonsmokers (table 1). A normal spirometry was observed in 3077 (91.8%) participants. Airflow obstruction was present in 214 (6.4%) subjects, of whom 119 (3.6%) were fixed. A possible isolated restrictive ventilatory impairment was present in 60 participants (1.8%).

SAD prevalence

Within the cohort, 425 participants (12.7%) had MMEF <65% PV and 167 participants (5.0%) had MMEF <LLN. None of the participants had MMEF <LLN and MMEF ⩾65% PV. Among 3077 participants (91.8%) with normal FEV_1/FVC ratio and normal FVC, 17 (0.6%) had MMEF <LLN compared to 201 (6.5%) with MMEF <65% PV. We observed similar results in the HNS population (n=1498, 44.7%), in which 17 (1.1%) had MMEF <LLN and 85 (5.7%) MMEF <65% PV. In the nonsmoker population (n=1665, 49.7%), 117 (7.0%) had MMEF <65% PV and 32 (1.9%) had MMEF <LLN. Among the 1366

TABLE 1 Baseline characteristics of individuals included in the PneumoLaus study (n=3351)

Age years, mean±SD	62.7±10.0
Female sex, n (%)	1865 (55.7)
Ever-smoked, n (%)	1686 (50.3)
Caucasian, n (%)	3273 (97.7)
Body mass index $kg \cdot m^{-2}$, mean±SD	26.4±4.7

TABLE 2 Summary of spirometry indices within the overall study population, ever-smoker population and nonsmoker population, and among participants with respiratory symptoms, asthma self-reported and COPD self-reported

	Overall	Ever-smoker	Nonsmoker	Respiratory symptoms	HNS	Asthma self-reported	COPD self-reported
Participants n	3351	1686	1665	214	1498	188	55
MMEF <65% PV, n (%)	425 (12.7)	308 (18.3)	117 (7.0)	67 (31.3)	85 (5.7)	59 (31.4)	35 (63.6)
MMEF <LLN, n (%)	167 (5.0)	135 (8.0)	32 (1.9)	38 (17.8)	17 (1.1)	38 (20.2)	26 (47.3)
FVC <LLN, n (%)	114 (3.4)	59 (3.5)	55 (3.3)	19 (8.9)	38 (2.5)	23 (12.2)	10 (18.2)
FEV_1/FVC <LLN, n (%)	189 (5.7)	147 (8.7)	42 (2.5)	33 (15.4)	28 (1.9)	36 (19.1)	25 (45.5)
FEV_1/FVC % PV, mean±SD	76.9±6.9	75.6±7.7	78.3±5.7	73.8±9.1	78.5±5.4	73.1±9.0	65.1±13.6
FEV_1 % PV, mean±SD	100.5±17.0	98.3±17.4	102.7±15.6	99.0±21.0	103.7±14.9	88.5±19.6	76.4±24.9
FVC % PV, mean±SD	101.7±14.4	100.1±14.5	102.4±14.3	94.1±16.8	103.1±13.9	94.3±16.4	89.4±17.6
MMEF % PV, mean±SD	104.4±36.8	98.8±37.6	110.1±35.1	87.7±39.0	111.8±34.5	80.1±34.9	63.9±47.1

Respiratory symptoms: subjects that report modified Medical Research Council dyspnoea scale ⩾2, cough or sputum. HNS: healthy nonsmokers; MMEF: maximum mid-expiratory flow; PV: predicted value; LLN: lower limit of normal; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s.

participants (39.9%) over 65 years, we observed 76 (5.6%) with MMEF <65% PV and 220 (16.25%) with MMEF <LLN.

Among the 95 participants (2.8%) with post-BD normalised spirometry, we observed 45 (47.4%) with MMEF <LLN and 80 (84.2%) with MMEF <65% PV. Among the 119 participants (3.6%) that had a fixed airflow obstruction, we detected MMEF <LLN in 94 individuals (79.0%) and MMEF <65% PV in 117 individuals (98.3%). 72.4% of participants with MMEF <65% PV and 80.8% with MMEF <LLN were ever-smokers. Table 2 summarises the prevalences for MMEF <LLN and MMEF <65% PV in the overall study population, in the population of ever-smokers, nonsmokers or those with respiratory symptoms.

Risk factors for SAD

We observed a significant association of MMEF <65% and MMEF <LLN criteria with tobacco consumption, duration of smoking, cough, sputum, dyspnoea, self-reported asthma and self-reported COPD (table 3). The association was highly significant between MMEF <LLN and at least the presence of one of the three symptoms cough, sputum or dyspnoea (OR 3.19, 95% CI 2.22–4.58). We observed a significant association with age only with MMEF <65% PV. We detected no association between MMEF <65% PV or <LLN and BMI. In addition, a positive association was present between MMEF (% pred) and BMI ($kg \cdot m^{-2}$) in the overall population ($p<0.01$).

Our model of logistic regression for age >65 years, duration of smoking, smoking status, sex, BMI and clinical variables found independent positive associations between smoking status, duration of smoking and dyspnoea with both MMEF <65% and MMEF <LLN criteria (figure 1). The association with age

TABLE 3 Association between MMEF <65% PV or MMEF <LLN with bivariate analysis for clinical features

	MMEF <65% PV			MMEF <LLN		
	Present	Absent	OR (95% CI)	Present	Absent	OR (95% CI)
Age years, mean (95% CI)	65.4 (64.4–66.4)	62.3 (61.9–62.6)	1.03 (1.02–1.04)	63.7 (62.1–65.3)	62.6 (62.3–62.9)	1.01 (0.99–1.03)
Age >65 years, n (%)	222 (52.2)	1144 (39.1)	1.70 (1.39–2.09)	76 (45.5)	1290 (40.5)	1.23 (0.90–1.68)
Duration of smoking (decade of years), mean (95% CI)	2.31 (2.13–2.49)	1.23 (1.17–1.29)	1.35 (1.28–1.42)	2.65 (2.37–2.93)	1.30 (1.24–1.36)	1.38 (1.29–1.48)
Female sex, n (%)	231 (54.4)	1634 (55.8)	0.94 (0.77–1.15)	89 (53.3)	1776 (55.8)	0.91 (0.67–1.25)
Ever-smoker, n (%)	308 (72.5)	1378 (47.1)	2.96 (2.35–3.72)	135 (80.8)	1551 (48.7)	4.44 (2.99–6.60)
Cough, n (%)	48 (11.3)	101 (3.5)	3.57 (2.48–5.13)	27 (16.2)	122 (3.8)	4.86 (3.09–7.65)
Sputum, n (%)	36 (8.5)	48 (1.6)	5.56 (3.55–8.72)	17 (10.2)	67 (2.1)	5.29 (3.02–9.27)
Dyspnoea mMRC ⩾1, n (%)	279 (65.7)	1337 (45.7)	2.31 (1.86–2.87)	121 (72.5)	1495 (47.0)	3.00 (2.11–4.27)
Asthma self-reported, n (%)	59 (13.9)	129 (4.4)	3.49 (2.51–4.86)	38 (22.8)	150 (4.7)	5.95 (3.98–8.91)
COPD self-reported, n (%)	35 (8.2)	20 (0.7)	13.04 (7.37–23.08)	26 (15.6)	29 (0.9)	20.06 (11.30–35.62)
Total, n (%)	425 (12.7)	2926 (87.3)	-	167 (5.0)	3184 (95.0)	-

MMEF: maximum mid-expiratory flow; PV: predicted value; LLN: lower limit of normal; OR: odds ratio; mMRC: modified Medical Research Council.

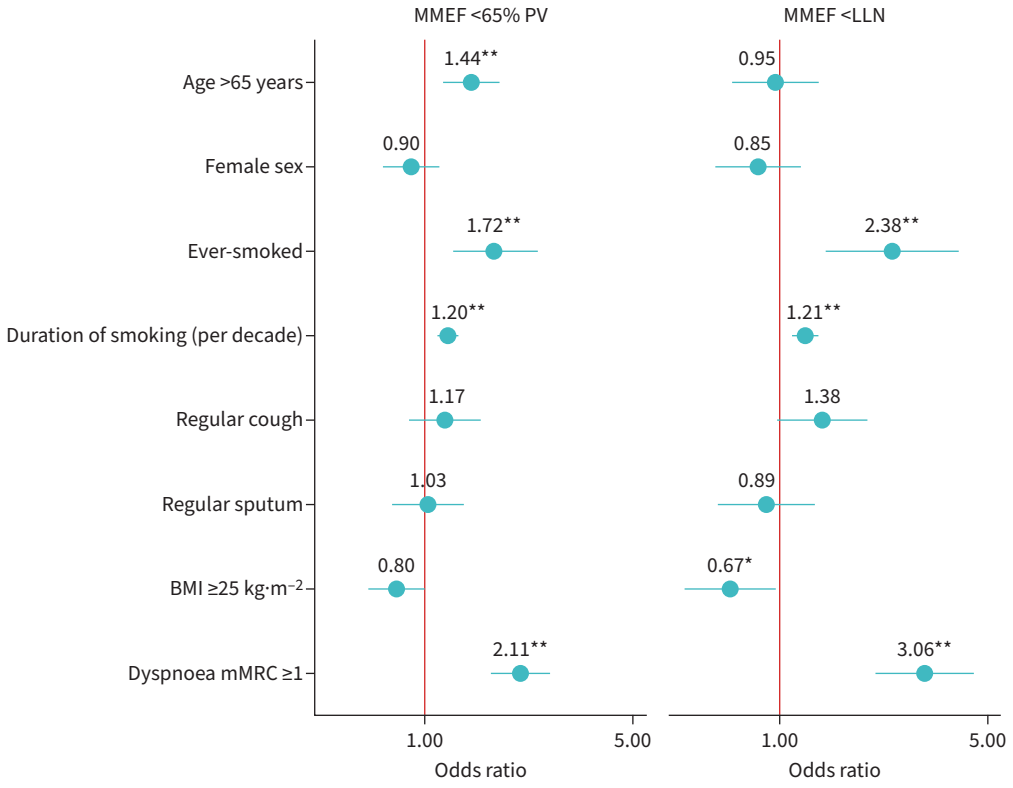

FIGURE 1 Association expressed as odds ratio between MMEF <65% PV or MMEF <LLN with logistic regression model adjusted for age, sex, ever-smoked, duration of smoking, regular cough, regular sputum, BMI and dyspnoea. MMEF: maximum mid-expiratory flow; PV: predicted value; LLN: lower limit of normal; BMI: body mass index; mMRC: Medical Research Council. *: p<0.05; **: p<0.01.

>65 years was only observed with MMEF <65% PV (OR 1.44, 95% CI 1.16–1.80). Also, we observed a negative association between MMEF <LLN and BMI employing the unit $kg \cdot m^{-2}$ ($p<0.01$) and categories >25 $kg \cdot m^{-2}$ (OR 0.67, 95% CI 0.48–0.94).

The Swiss FOEN reports mean population weighted $PM_{2.5}$ and PM_{10} ambient concentrations of 14.1 $\mu g \cdot m^{-3}$ and 19.4 $\mu g \cdot m^{-3}$ in 2010, respectively. $PM_{2.5}$ and PM_{10} originated from transport (24% and 17%), industry (26% and 28%), household /commercial (22% and 37%), agriculture and forestry (27% and 18%), respectively. In Lausanne, the mean annual particulate matter air concentration varied from 12.2 to 22.6 $\mu g \cdot m^{-3}$ between 2010 and 2020 for PM_{10}, and from 6.3 to 9.2 $\mu g \cdot m^{-3}$ between 2017 and 2020 for $PM_{2.5}$ (supplementary table S1) [33, 34].

Discussion

We observed a SAD prevalence of respectively 12.7% and 5.0% depending on the defining criteria of MMEF <65% PV and MMEF <LLN. Based on MMEF <65% PV criteria, 5.7% of HNS, 7.0% of nonsmokers and 6.5% of those with normal FEV_1/FVC ratio and normal FVC met the definition of SAD. These rates are close to 5% and thus coherent with the assumption that PFT results are abnormal when below the 5th percentile of the GLI-2012 reference values. Interestingly, the prevalence of SAD is 5.0% in the overall population using the MMEF <LLN criteria, corresponding to the theoretical definition of LLN. Moreover, using a criterion based on the LLN is in accordance with current practice [12] and recommended in a recent systematic review [6].

Participants with MMEF <LLN reported more respiratory symptoms such as dyspnoea, cough or sputum than those with MMEF <65% PV who had a higher rate of respiratory impairment with fixed airflow obstruction or post-BD normalised spirometry. Utilising MMEF <LLN, the SAD prevalence of 0.6% in healthy nonsmoking individuals, 1.9% in nonsmokers and 1.1% in participants with normal spirometry suggests an underestimation of SAD and thus avoids overdiagnosis in this population. Conversely, using

the MMEF <65% PV criteria may lead to overdiagnosis of SAD, particularly in the elderly population, where we observed no association between the MMEF <LLN criteria and age. Such overdiagnosis related to utilisation of the MMEF <65% PV criteria may be explained by an increasing dispersion around the mean with age similarly to FEV_1/FVC, as described for GLI-2012 [30].

Our SAD prevalence was lower than the 43.5% reported by a recent cross-sectional national study by Xiao *et al*. [9] with a similar proportion of never-smokers, but younger and less overweight participants, employing the presence of at least two of three defining criteria for SAD (FEF_{50} <65% PV, FEF_{75} <65% PV, MMEF <65% PV). We used less rigorous criteria. Another Asian population study detected a higher prevalence of SAD of 30% [10]. Using the same MMEF <LLN criteria, our prevalence of SAD is close to, but slightly lower than, the European prevalence reported in the BOLD study with 14.3% (5% in Estonia, 9% in Sweden, 9% in Germany,15% in Austria and 23% in Turkey) [7]. Of note, the BOLD study analysed data in 8751 participants from 14 European sites, compared to our study population of 3351 participants.

In our study, 50.3% of participants were former or current smokers. This proportion is lower than in other comparable studies such as the Swiss study on Air Pollution and Respiratory Diseases in Adults (SAPALDIA) [36] or the Rotterdam Study [37], which reported rates of 64.2% and 63.4%, respectively. The rates of ever-smokers were also higher in Hannover (70.0%) and in Salzburg (59.4%) as reported by Buist *et al*. [38], which are comparable to the 71.4% reported by Xiao *et al*. [9]. However, the rate of ever-smokers reported by the ERS spirometry tent study (48.8%) [39] was similar to ours. The comparatively lower rate of ever-smokers in PneumoLaus might partly explain the lower prevalence of fixed airflow obstruction and underscores the robustness of our estimation of SAD prevalence by MMEF spirometric measurement in a general population without airflow obstruction.

GLI-2012 reference values used in our study are based on 97 759 HNS, whereas reference values utilised in the study by Xiao *et al*. stem from a smaller population of 7115 HNS [30, 40]. However, a recent study based on a Northeast Asian population identified similar prevalence of SAD using the GLI-2012 reference [18].

We did not find an association between SAD prevalence and high BMI by category or as a continuous variable in PneumoLaus. In contrast to the study by Xiao *et al*. [9], we did not identify obesity or overweight as risk factors for SAD. This may be explained by a different prevalence of obesity or overweight in our cohort (48.5%), as compared to the 36.1% reported by Xiao *et al*. [9]. Also, GLI equations might have a superior predictive accuracy of MMEF with higher weight.

Furthermore, in our adjusted multivariable analysis we observed a significant negative association between BMI as continuous or categorical variable and the prevalence of SAD as defined by MMEF <LLN, but not with the criteria MMEF <65% PV. This negative association was already observed in the BOLD study [7]. One explanation could be that high BMI increases extra-thoracic pressure, thus accelerating air expulsion and subsequently increasing MMEF independently of the presence of a clinically relevant SAD. With a higher MMEF in the obese population, the prevalence of SAD defined by MMEF could therefore be decreased. We observed a positive association with SAD defined by MMEF <65% PV and age, but not when using MMEF <LLN criteria. The observed association with MMEF <65% PV is present when using a categorical division of age of 65 years.

After adjusting for the above-discussed risk factors for SAD, ethnicity and air pollution may contribute to the large difference in SAD prevalence between the results reported in studies from Xiao *et al*. [9] and Xing *et al*. [18], as compared to data from our study and the BOLD study [7]. To date, no other European study has analysed the association between local air pollution levels and SAD. Lifestyle, especially regarding diet, might also impact our results compared to the Xiao *et al*. and Xing *et al*. studies [41–43].

The population weighted exposure in Switzerland to $PM_{2.5}$ was low during the study as well as in the geographical area where the cohort study was carried out. Exposure of PM_{10} was also low before and during the study. Furthermore, based on a modelling approach, 86.9% of the Swiss population had a mean annual $PM_{2.5}$ exposure <15 $\mu g \cdot m^{-3}$ and no mean annual exposure >25 $\mu g \cdot m^{-3}$ in 2005, 2010 and 2020 [33]. The mean national exposure for Switzerland contrasts with the annual mean $PM_{2.5}$ exposure of over 50 $\mu g \cdot m^{-3}$ reported for 92.6% of participants in the study by Xiao *et al*. [9]. Difference in the $PM_{2.5}$ exposure may therefore partly explain the differences in SAD prevalence between this study and ours. In an area with low $PM_{2.5}$ exposure, smoking appears to be the main factor associated with SAD.

Our study has several limitations. First, we did not measure the individual mean exposure of participants to $PM_{2.5}$ and PM_{10} during our study and employed the mean national and local exposure in 2010 and 2020 as an approximation. Second, with a proportion of 97.7% Caucasians in PneumoLaus, we could not analyse the impact of ethnicity on SAD, and our conclusions apply only to the Caucasian population. Third, age was not evenly distributed in our population with relatively lower numbers of young participants (subjects <50 years=373). The participants underwent spirometry only during the visit, and our study did not capture MMEF variation over time, which may be useful to follow development of SAD in susceptible individuals.

Conclusion

We herein provide evidence for a lower prevalence of SAD in a European urban general population as compared to data stemming from Asia, a difference likely related to lower $PM_{2.5}$ exposure, ethnicity or lifestyle. Furthermore, employing the MMEF <65% PV criteria may lead to overdiagnosis of SAD in the elderly population in which the MMEF <LLN may be more precise. We consider the MMEF <LLN criterion to be more accurate. In an area with low $PM_{2.5}$ exposure smoking appears to be the main factor associated with SAD. Our results highlight the need for future national and international coordinated strategies focused on preservation and improvement of air quality as a determinant for respiratory health.

Provenance: Submitted article, peer reviewed.

Acknowledgements: The authors thank the participants of the study as well as Antigone Askitoglu (Division of Pulmonology, Department of Medicine, Lausanne University Hospital (CHUV), and University of Lausanne (UNIL), Lausanne, Switzerland), lung function technician, who performed all spirometries and oversaw the completion of all questionnaires. We thank Gérard Waeber (Division of Internal Medicine, Department of Medicine, CHUV and UNIL, Lausanne, Switzerland) for his valued advice for the manuscript.

Conflict of Interest: J. Vaucher reports receiving grants or contracts from Swiss National Science Foundation grant 3247730_204523, Fondation Leenaards, AGLA funding and Fondation pour la Recherché Contre le Diabète, outside the submitted work. C. von Garnier reports grants or contracts from OM Pharma, outside the submitted work; consulting fees from AstraZeneca, GSK, Boehringer Ingelheim and OM Pharma, outside the submitted work; and payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from AstraZeneca, GSK and OM Pharma, outside the submitted work. The remaining authors have nothing to disclose.

Support statement: This study was supported by GlaxoSmithKline, the Faculty of Biology and Medicine of Lausanne, and the Swiss National Science Foundation grants 3247730_204523, 33CS30-139468, 33CS30-148401, 33CS30_177535 and 33CSCO-122661. Funding information for this article has been deposited with the Crossref Funder Registry.

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