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Prevalence of small airway dysfunction in the Swiss PneumoLaus Cohort

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Take-Home Message
We report a prevalence of small airway dysfunction (SAD)≤12.7% in an area with low air pollution levels. A low prevalence of SAD was associated with lower PM⁰.⁵ exposure. MMEF <65% PV criteria carries a risk of overdiagnosing SAD in elderly individuals.
Abstract

**Background** Recent evidence identified exposure to particulate matter of size \(<2.5 \mu m (PM_{2.5})\) 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, gender, body mass index (BMI), respiratory symptoms, and smoking status. Mean PM$_{2.5}$ values were obtained from a Swiss national database.

**Results** Among 3351 participants (97.6% Caucasian, 55.8% 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 \(\geq 65\%\) PV. MMEF <65% PV and MMEF < LLN were significantly associated with age, smoking status, cough, sputum, 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 µg/m$^3$ during the observation period (2010 and 2020), \(\geq 72\%\) 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 the elderly individuals.

**Key words:** small airways, small airway dysfunction, particulate matter, Spirometry, pollution, lung function in epidemiology

Abstract: 251 words

Main body: 3097 words
Introduction

Early changes associated with airway diseases are thought to occur in small and distal airways. Therefore, there has been increasing interest over 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\(^\%\), and a recent review described a prevalence between 7.5 and 45.9\(^\%\). In addition, Brenner et al. reported a SAD prevalence of 25\(^\%\) in patients with stable heart failure (n=585)\(^8\). In contrast, population-based studies from Asia reported high rates of SAD. Xiao et al. report a prevalence of 43.5\(^\%\) estimated out of a population of 53'546 individuals\(^9\) and Kwon et al. estimate the prevalence at 30\(^\%\) among 3'624 participants\(^10\).

Despite the wide availability of spirometry, there is currently no accepted gold standard to diagnose SAD\(^1\)\(^,\)\(^6\)\(^,\)\(^11\). Forced expiratory volume in 1 second (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 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\(^18\)\(^,\)\(^9\). 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\(^10\)\(^,\)\(^22\), alpha-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. identified exposure to particulate matter of size ≤2.5 µm (PM\(_{2.5}\)) as a possible risk factor for the high prevalence of SAD\(^9\), along with smoking and a body mass index (BMI) ≥25 kg/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\(^\text{27,28}\). 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\(^\text{29}\). The GLI-2012 reference values were used, adjusting for ethnicity\(^\text{30}\). 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\(^\text{31}\). 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\(^\text{32}\).

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\(^\text{28}\). The presence of a FVC below LLN before BD that normalised after BD was also classified as a post-BD normalised spirometry because we suspected air trapping\(^\text{31}\). SAD was defined by maximum mid-expiratory flow (MMEF) before BD <65% PV or MMEF < LLN utilising GLI-2012 references values\(^\text{30}\).

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. Healthy non-smokers (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.

**Statistical analyses**

Participant characteristics were expressed as number (percentage) for categorical variables, and as mean with standard deviation (SD) or 95% confidence interval (CI 95%) for continuous variables. Between-group comparisons were performed utilising chi-square, student's 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 significantly covariates as independent variables. MMEF ≥65% PV or MMEF ≥ LLN was considered the reference, and results were expressed as odds ratio and 95% confidence interval. 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. The mean BMI was 26.4 (SD = 4.7) kg/m$^2$, 1329 (39.9%) subjects had a normal BMI, 55 (1.7%) were underweight, 1346 (40.4%) were overweight and 603 (18.1%) were obese, according to the WHO classification. There was a slight female preponderance (n = 1845, 55.8%), 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 non-smokers (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 FEV1/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 non-smoker population (n = 1665, 49.7%), 117 (7.0%) had MMEF <65% PV and 32 (1.9%) had MMEF < LLN. Among the 1366 participants (39.9%) over 65 years, we observed 76 (5.6%) with MMEF <65% PV and 32 (1.9%) had 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 eversmokers. Table 2 summarises the prevalences for MMEF < LLN and MMEF <65% PV in the overall study population, in the population of eversmokers, non-smokers or 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, CI 95% [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 (percent predicted) and BMI (kg/m²) in the overall population (p < 0.01).

Our model of logistic regression for age > 65 years, duration of smoking, smoking status, gender, 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 > 65 years was only observed with MMEF <65% PV (OR 1.44, CI 95% [1.16-1.80]). Also, we observed a negative association between MMEF < LLN and BMI employing the unit kg/m² (p < 0.01) and categories > 25 kg/m² (OR 0.67, CI 95% [0.48-0.94]).

The Swiss FOEN reports average population weighted PM$_{2.5}$ and PM$_{10}$ ambient concentrations of 14.1 µg/m$^3$ and 19.4 µg/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 average annual particulate matter air concentration varied from 12.2 to 22.6 µg/m$^3$ between 2010 and 2020 for PM$_{10}$, and from 6.3 to 9.2 µg/m$^3$ between 2017 and 2020 for PM$_{2.5}$ (Table 1 supplementary)$^{33,34}$.

**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 non-smokers and 6.5% of those with normal FEV1/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 fifth 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\textsuperscript{12} and recommended in a recent systematic review\textsuperscript{6}.

Participants with MMEF < LLN reported more respiratory symptoms such as dyspnoea, cough or sputum, than those with MMEF <65% PV that 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 non-smoking individuals, 1.9% in non-smokers 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\textsubscript{1}/FVC, as described for GLI-2012\textsuperscript{20}.

Our SAD prevalence was lower than the 43.5% reported by a recent cross-sectional national study by Xiao et al. with a similar proportion of never smokers, but younger and less overweight participants, employing the presence at least two of three defining criteria for SAD (FEF\textsubscript{50} <65% PV, FEF\textsubscript{75} <65% PV, MMEF<65% PV).\textsuperscript{9} We used less rigorous criteria. Another Asian population study detected a SAD higher prevalence of 30%\textsuperscript{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).\textsuperscript{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)\textsuperscript{36} or the Rotterdam Study\textsuperscript{37} that 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.\textsuperscript{38}, which are comparable to the 71.4% reported by Xiao et al.\textsuperscript{9}. However, the rate of ever smokers reported by the ERS spirometry tent study (48.8%) was similar\textsuperscript{29} 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 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\textsuperscript{30,40}. However, a recent study based on a North East Asian population identified similar prevalence of SAD using GLI-2012 reference\textsuperscript{18}.

We did not find an association between SAD prevalence and high BMI by category or as continuous variable in PneumoLaus. In contrast to the study by Xiao et al.\textsuperscript{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.\textsuperscript{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. 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 large difference in SAD prevalence between the results reported in studies from Xiao et al. and Xing et al., as compared to data from our and from the BOLD study. 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 their studies.

The population weighted exposure in Switzerland to PM was low during study as well as in the geographic area where the cohort study was undergone. Exposure of PM 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 exposure < 15 µg/m³ and no mean annual exposure > 25 µg/m³ in 2005, 2010, and 2020. The mean national exposure for Switzerland contrasts the annual mean PM exposure over 50 µg/m³ reported for 92.6% of participants in the study of Xiao et al.. Difference in the PM exposure may therefore partly explain the differences in SAD prevalence between this study and ours. In an area with low PM 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 and PM 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 that 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 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 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.
Acknowledgements

The authors thank the participants of the study as well as Ms. 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 Prof. Gérard Waeber (Division of Internal medicine, Department of Medicine, Lausanne University Hospital (CHUV), and University of Lausanne (UNIL), Lausanne, Switzerland) for his valued advice for the manuscript.

Table 1. Baseline characteristics of individuals included in the PneumoLaus study.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall, n = 3351</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years], mean (SD)</td>
<td>62.7 (10.0)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>1865 (55.8)</td>
</tr>
<tr>
<td>Ever smoked, n (%)</td>
<td>1686 (50.3)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>3273 (97.7)</td>
</tr>
<tr>
<td>BMI [kg/m²], mean (SD)</td>
<td>26.4 (4.7)</td>
</tr>
</tbody>
</table>

BMI = Body Mass Index.
Table 2. Summary of spirometry indices within the overall study population, ever smoker population, non-smoker population, and among participants with respiratory symptoms, asthma self-reported and COPD self-reported.

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 3351)</th>
<th>Ever smoker (n = 1686)</th>
<th>Non-smoker (n = 1665)</th>
<th>Respiratory symptoms (n = 214)</th>
<th>HNS (n = 1498)</th>
<th>Asthma self-reported (n = 188)</th>
<th>COPD self-reported (n = 55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMEF &lt;65% PV, n (%)</td>
<td>425 (12.7)</td>
<td>308 (18.3)</td>
<td>117 (7.0)</td>
<td>67 (31.3)</td>
<td>85 (5.7)</td>
<td>59 (31.4)</td>
<td>35 (63.6)</td>
</tr>
<tr>
<td>MMEF &lt; LLN, n (%)</td>
<td>167 (5.0)</td>
<td>135 (8.0)</td>
<td>32 (1.9)</td>
<td>38 (17.8)</td>
<td>17 (1.1)</td>
<td>38 (20.2)</td>
<td>26 (47.3)</td>
</tr>
<tr>
<td>FVC &lt; LLN, n (%)</td>
<td>114 (3.4)</td>
<td>59 (3.5)</td>
<td>55 (3.3)</td>
<td>19 (8.9)</td>
<td>38 (2.5)</td>
<td>23 (12.2)</td>
<td>10 (18.2)</td>
</tr>
<tr>
<td>FEV1/FVC &lt; LLN, n (%)</td>
<td>189 (5.7)</td>
<td>147 (8.7)</td>
<td>42 (2.5)</td>
<td>33 (15.4)</td>
<td>28 (1.9)</td>
<td>36 (19.1)</td>
<td>25 (45.5)</td>
</tr>
<tr>
<td>FEV1/FVC [% PV], mean, (SD)</td>
<td>76.9 (6.9)</td>
<td>75.6 (7.7)</td>
<td>78.3 (5.7)</td>
<td>73.8 (9.1)</td>
<td>78.5 (5.4)</td>
<td>73.1 (9.0)</td>
<td>65.1 (13.6)</td>
</tr>
<tr>
<td>FEV₁ [% PV], mean (SD)</td>
<td>100.5 (17.0)</td>
<td>98.3 (17.4)</td>
<td>102.7 (15.6)</td>
<td>99.0 (21.0)</td>
<td>103.7 (14.9)</td>
<td>88.5 (19.6)</td>
<td>76.4 (24.9)</td>
</tr>
<tr>
<td>FVC [% PV], mean (SD)</td>
<td>101.7 (14.4)</td>
<td>100.1 (14.5)</td>
<td>102.4 (14.3)</td>
<td>94.1 (16.8)</td>
<td>103.1 (13.9)</td>
<td>94.3 (16.4)</td>
<td>89.4 (17.6)</td>
</tr>
<tr>
<td>MMEF [% PV] mean (SD)</td>
<td>104.4 (36.8)</td>
<td>98.8 (37.6)</td>
<td>110.1 (35.1)</td>
<td>87.7 (39.0)</td>
<td>111.8 (34.5)</td>
<td>80.1 (34.9)</td>
<td>63.9 (47.1)</td>
</tr>
</tbody>
</table>

Respiratory symptoms = subjects that report dyspnoea mMRC ≥2, cough or sputum; MMEF = Maximum Mid-Expiratory Flow; PV = Predicted Value; HNS = Healthy Non-Smokers; LLN = Lower Limit of Normal; SD = Standard Deviation; FEV₁ = Forced Expiratory Volume in 1 second, FVC = Forced Vital Capacity, COPD = Chronic Obstructive Pulmonary Disease.
Table 3. Association between MMEF <65% PV or MMEF < LLN with bivariate analysis for clinical features.

<table>
<thead>
<tr>
<th></th>
<th>MMEF &lt;65% PV</th>
<th></th>
<th>MMEF &lt; LLN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present</td>
<td>Absent</td>
<td>OR [CI 95%]</td>
</tr>
<tr>
<td>Age [years], mean [CI 95%]</td>
<td>65.4 [64.4-66.4]</td>
<td>62.3 [61.9-62.6]</td>
<td>1.03 [1.02-1.04]</td>
</tr>
<tr>
<td>Age &gt; 65 years, n (%)</td>
<td>222 (52.2)</td>
<td>1144 (39.1)</td>
<td>1.70 [1.39-2.09]</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>231 (54.5)</td>
<td>1634 (56.0)</td>
<td>0.94 [0.77-1.15]</td>
</tr>
<tr>
<td>Ever smoker, n (%)</td>
<td>308 (72.5)</td>
<td>1378 (47.1)</td>
<td>2.96 [2.35-3.72]</td>
</tr>
<tr>
<td>Cough, n (%)</td>
<td>48 (11.3)</td>
<td>101 (3.5)</td>
<td>3.57 [2.48-5.13]</td>
</tr>
<tr>
<td>Sputum, n (%)</td>
<td>36 (8.5)</td>
<td>48 (1.6)</td>
<td>5.56 [3.55-8.72]</td>
</tr>
<tr>
<td>Dyspnoea mMRC ≥ 1, n (%)</td>
<td>279 (66.3)</td>
<td>1337 (46.0)</td>
<td>2.31 [1.86-2.87]</td>
</tr>
<tr>
<td>Asthma self-reported, n (%)</td>
<td>59 (13.9)</td>
<td>129 (4.4)</td>
<td>3.49 [2.51-4.86]</td>
</tr>
<tr>
<td>COPD self-reported, n (%)</td>
<td>35 (8.2)</td>
<td>20 (0.7)</td>
<td>13.01 [7.37-23.08]</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>425 (12.7)</td>
<td>2926 (87.3)</td>
<td>-</td>
</tr>
</tbody>
</table>
References


Figure 1

- Age > 65 years: 1.44**
- Female sex: 0.90
- Ever smoked: 1.72**
- Duration of smoking (per decade): 1.20**
- Regular cough: 1.17
- Regular sputum: 1.03
- BMI ≥ 25 kg/m²: 0.80
- Dyspnoea mMRC ≥ 1: 2.11**

MMEF < LLN
- Age > 65 years: 0.95
- Female sex: 0.85
- Ever smoked: 1.21**
- Duration of smoking (per decade): 1.38
- Regular cough: 0.89
- Regular sputum: 0.89
- BMI ≥ 25 kg/m²: 0.67*
- Dyspnoea mMRC ≥ 1: 3.06**

* p < 0.05
** p < 0.01
**Supplementary Table 1.** Mean annual air concentration of PM$_{2.5}$ between 2017 and 2020, and PM$_{10}$ between 2010 and 2020, in city of Lausanne. Specific measure of PM$_{2.5}$ only started in Lausanne in 2017

<table>
<thead>
<tr>
<th>Year</th>
<th>PM$_{10}$ [µg/m$^3$]</th>
<th>PM$_{2.5}$ [µg/m$^3$]</th>
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</thead>
<tbody>
<tr>
<td>2010</td>
<td>20.4</td>
<td>N/A</td>
</tr>
<tr>
<td>2011</td>
<td>22.6</td>
<td>N/A</td>
</tr>
<tr>
<td>2012</td>
<td>19.2</td>
<td>N/A</td>
</tr>
<tr>
<td>2013</td>
<td>20.3</td>
<td>N/A</td>
</tr>
<tr>
<td>2014</td>
<td>15.7</td>
<td>N/A</td>
</tr>
<tr>
<td>2015</td>
<td>17.8</td>
<td>N/A</td>
</tr>
<tr>
<td>2016</td>
<td>14.1</td>
<td>N/A</td>
</tr>
<tr>
<td>2017</td>
<td>12.2</td>
<td>6.3</td>
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<tr>
<td>2018</td>
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<tr>
<td>2019</td>
<td>14.3</td>
<td>8.3</td>
</tr>
<tr>
<td>2020</td>
<td>12.4</td>
<td>7.8</td>
</tr>
</tbody>
</table>

PM$_{10}$ = Particulate Matter of size ≤ 10 µm; PM$_{2.5}$ = Particulate Matter of size ≤ 2.5 µm; N/A = Not Available