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# Distinct Lung Function Phenotypes in Never-Smokers with Chronic Airflow Limitation

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## Abstract

# Background

Chronic airflow limitation (CAL) is often caused by smoking, but a proportion of subjects have never smoked. The definition of CAL is based on airway obstruction measured by spirometry, but the pathophysiology behind airway obstruction in never-smokers is poorly known. We aimed to investigate CAL (defined as FEV1/FVC < 0.7) in never-smokers employing comprehensive lung function measurements.

# Methods

Never-smokers with CAL with FEV1/FVC < or ≥ lower limit of normal (LLN) and FEV1 < or ≥ 100% of the predicted value were included: 35 with $CAL_{< LLN, FEV1<100}$, 30 with $CAL_{\geq LLN, FEV1<100}$, and 26 with $CAL_{FEV1\geq100}$. In addition, 41 never-smokers and 23 smokers, with normal spirometry were used as controls. Pre- and postbronchodilator spirometry, respiratory oscillometry, body plethysmography and measurements of diffusing capacity were performed. Respiratory symptom burden was recorded.

# Results

Never-smokers with $CAL_{< LLN, FEV1<100}$ showed a mild lung function impairment measured by spirometry, but with lung volumes, diffusing capacity and airway resistance within normal range, and presented no increase in respiratory symptoms. They had, however, an increased bronchodilator responsiveness in airway resistance and reactance, most pronounced in the peripheral airways. In contrast, in the group with $CAL_{FEV1\geq100}$, lung volumes and diffusing capacity were increased, while airway resistance was at the same level as in never-smokers without CAL. $CAL_{\geq LLN, FEV1<100}$, presented between those with $CAL_{< LLN, FEV1<100}$ and $CAL_{FEV1\geq100}$.

# Conclusions

CAL with lowered FEV1 in never-smokers constitutes a phenotype with milder lung function impairment, predominantly affecting the small airways, whereas subjects with a reduced FEV1/FVC ratio due to supranormal lungs do not have other signs of pathological lung physiology.

## INTRODUCTION

Chronic Airflow Limitation (CAL) is a persistent reduction in expiratory airflow that reflects structural and functional abnormalities within the respiratory system. Characterized by a non-fully reversible

obstruction of the airways, CAL represents a major pathophysiological feature of several chronic respiratory diseases, most notably chronic obstructive pulmonary disease (COPD)[1].

CAL is typically quantified using spirometry, where a reduced ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) < 0.7 after bronchodilator defines persistent airflow obstruction. There is an ongoing discussion on whether CAL should be defined based on the fixed ration of FEV1/FVC < 0.7, or below lower limit of normal (LLN) of FEV1/FVC[2, 3]. Using a fixed ratio is a clinically more accessible cut-off as it is simple and independent on reference values and is thereby recommended in the GOLD reports[1, 4]. In contrast, the use of LLN as cut-off is considered to be more accurate as it takes age-related lung function deterioration into account[5]. Regardless of whether fixed ratio or LLN is used, the overarching concern is the under-use of spirometry in detecting COPD.

CAL is a hallmark and mandatory for diagnosing COPD[6] and can arise from several different conditions and can be found in different parts of the airways, and usually with a pathological cause. Risk factors may include tobacco smoke or exposure to other particles, as well as genetic factors or early life events[7]. Other known conditions that can cause CAL are asthma, bronchiectasis and advanced age. People with habitually large lungs[8, 9] might have a low FEV1/FVC ratio and, thus, by definition a CAL. The explanation for this could be that it is physically impossible for someone with a large lung capacity to exhale 70% or more of their vital capacity during the first second. However, presence of respiratory symptoms such as dyspnoea, wheeze, cough and/or a history of lower airway infections in combination with exposure to risk factors, increase the likelihood for having COPD[6].

While exposure to tobacco smoke is the most common risk factor for developing COPD, population-based studies have found 7–40% never-smokers among those with COPD[10–12]. In a recent Swedish large population study, 9% of never-smokers was classified as having CAL[13]. COPD in never-smokers seems to have a greater burden of airway symptoms compared with healthy individuals, along with a higher prevalence of comorbidities[13–15]. In contrast, they experience milder respiratory symptoms, fewer exacerbations and reduced mortality risk than ever-smokers with COPD, but higher rates compared to healthy individuals[3, 10–12]. This phenotype of COPD has consequently been excluded in clinical trials. Therefore, there is a significant lack of knowledge about this group, both when it comes to drug treatments and other characteristics, such as detailed investigation of their lung physiology.

Previous studies on CAL in never-smokers[10, 16, 17] have mostly used only spirometry and have not undertaken a detailed mapping of the lower airways with both body plethysmography and impulse oscillometry.

# MATERIAL AND METHODS

## Aim

The main aim of the present study was to thoroughly examine chronic airflow limitation using different advanced lung function measurements in never-smokers with CAL compared to controls.

## Subjects

The cohort was recruited from the previous large population-based, multi-centre Swedish Cardiopulmonary bioimage study (SCAPIS)[18], and included in the present sub-study, BRONCHO-SCAPIS[19], (www.clinicaltrials.gov/study/NCT03049202). Participants in this analysis were categorized into five groups based on lung function after bronchodilatation as presented in Table 1. Three of the groups had CAL, which was defined as having an $FEV_1$/FVC ratio < 0.7. For two of the groups with CAL, the further division was based upon a z-score for the obstructive ratio < or ≥ lower limit of normal (LLN; < or ≥ -1.64 standard deviations (SD)) and an FEV1 < 100% of predicted (%pred), i.e. $\mathbf{CAL_{< LLN,\ FEV1<100}}$ and $\mathbf{CAL_{\geq LLN,\ FEV1<100}}$. The third group with CAL required a FEV1/FVC ratio < 0.7 regardless of z-score but an FEV1 ≥ 100%pred ($\mathbf{CAL_{FEV1\geq100}}$). The control groups consisted of healthy never-smokers (**HNS**) and smoking controls (**SC**), both groups with an $FEV_1$/FVC ratio ≥ 0.7 and an FEV1 ≥ 90%pred. In the control groups, only those with FEV1 ≥ 90%pred were included to avoid individuals within the lower normal range.

Table 1
Classification of subjects according to smoking status and post-bronchodilator spirometry results

| **Description** | **Smoking status** | **$FEV_1$/FVC, ratio** | **$FEV_1$/FVC, z-score** | **$FEV_1$, %pred** |
|---|---|---|---|---|
| Healthy never-smokers (HNS) | Never[a] | ≥ 0.70 | ≥-1.64 | ≥ 90% |
| Never-smokers with $CAL_{< LLN, FEV1<100}$ | Never[a] | < 0.70 | < -1.64 | < 100% |
| Never-smokers with $CAL_{\geq LLN, FEV1<100}$ | Never[a] | < 0.70 | ≥-1.64 | < 100% |
| Never-smokers with $CAL_{FEV1\geq100}$ | Never[a] | < 0.70 | No limit | ≥ 100% |
| Smoking controls (SC) | Current with ≥ 10 pack-years | ≥ 0.70 | ≥-1.64 | ≥ 90% |

[a] <100 cigarettes in total and no smoking for the last 2 years.

**Abbreviations:** CAL=chronic airflow limitation (i.e. $FEV_1$/FVC<0.7); $FEV_1$=Forced Expiratory Volume in one second; FVC=Forced Vital Capacity; %pred=% of predicted normal; LLN=Lower limit of normal Never-smokers were defined as having smoked < 100 cigarettes or < 20 cigars during their lifetime and not smoked at all during the last 2 years. Smokers were defined as currently smoking individuals (at least 10 cigarettes per day) with a smoking history of ≥ 10 pack-years. All subjects performed comprehensive lung function testing, measured using spirometry, body plethysmography, diffusing capacity and impulse oscillometry (IOS) as described below. A digital questionnaire was used to include detailed background information about smoking habits and doctor's diagnosed asthma. All participants were interviewed to confirm the absence of any current or past respiratory diseases other than COPD or asthma.

The study was conducted between 2018 and 2023 at two University Hospitals in Sweden: Sahlgrenska University Hospital in Gothenburg and Skåne University Hospital in Lund. A total of 100 never-smokers were enrolled in Gothenburg, Sweden, while 32 never-smokers and 23 current healthy smokers were enrolled in Lund, Sweden.

## Pulmonary function tests

All participants were asked to refrain from short- and long-acting bronchodilators for ≥ 4 hours and ≥ 12 hours, respectively, prior to the tests. Pre-bronchodilator IOS and spirometry were performed, and IOS was performed before spirometry to minimize the effect of forced spirometry manoeuvres on the bronchial tone. The subjects thereafter inhaled 0.4 mg of Salbutamol (Ventoline Evohaler©, GlaxoSmithKline AB, Solna, Sweden). Post-bronchodilator measurements were performed a minimum of 15 minutes (maximum 45 minutes) after the inhalation and included IOS, spirometry, body plethysmography and diffusing capacity test. Bronchodilator responsiveness was calculated as % of change from baseline [=(post-bronchodilator – pre-bronchodilator) / pre-bronchodilator x100] of values from measurements by spirometry and IOS. Subjects were defined as bronchodilator responsive in FEV1 or FVC if having a ≥ 12% and ≥ 200 ml increase in FEV1 and/or FVC, respectively, from pre- to post-bronchodilator tests[20].

IOS was performed with the subjects sitting upright, wearing a nose clip and breathing tidally through a bacterial mouthpiece/filter while pressing their palms against the cheeks to minimize upper airway shunting. Respiratory, inspiratory and expiratory, resistance at 5 Hz (R5, $R5_{insp}$ and $R5_{exp}$) and 20 Hz (R20, $R20_{insp}$ and $R20_{exp}$), the difference between R5 and R20 (R5-R20), and respiratory, inspiratory, and expiratory reactance at 5 Hz (X5, $X5_{insp}$ and $X5_{exp}$) were examined[21], as was resonant frequency ($F_{res}$) and area under reactance curve (AX)[22, 23].

FEV1 and FVC were measured using a spirometer, and spirometry manoeuvres were performed according to the standards recommended by the American Thoracic Society/European Thoracic Society[24, 25]. Lung volumes (total lung capacity, TLC, vital capacity, VC, residual volume, RV, functional

residual capacity, FRC and inspiratory capacity, IC) and airway resistance (total, $R_{tot}$, inspiratory, $R_{insp}$ and expiratory, $R_{exp}$) were measured using body plethysmography[26]. Diffusing capacity of the lung ($D_{LCO}$), alveolar volume ($V_A$) and Carbon monoxide transfer coefficient ($K_{CO}$) were measured using single breath technique[27].

The IOS system used was a Master Screen IOS (Erich Jaeger GmbH, Würzburg, Germany). Spirometry was performed using Master Screen, (Erich Jaeger GmbH). Body plethysmography (Master Screen Body, Erich Jaeger GmbH) and measurements of $D_{LCO}$ (Master Screen PFT, Erich Jaeger GmbH) were solely performed post-bronchodilator.

All reference values for spirometry, body plethysmography and $D_{LCO}$ were taken from the Global Lung Function Initiative (GLI)[28], and z-scores and percent predicted values were calculated using the calculator at the GLI website (ref http://gli-calculator.ersnet.org/) overall using Caucasian as ethnic. Reference values for IOS were those presented by Oostveen et al. [29]. Due to technical issues, all tests could not be performed by all subjects, so the exact numbers are given in the tables.

## Symptom scoring

To evaluate symptoms, the COPD Assessment Test (CAT)[30] was completed by all subjects, and the results are presented as total scores.

# Statistical analysis

Results are presented as median and interquartile range (IQR), unless otherwise stated. Graphical presentations, using box plots, show the results for all groups presented using GraphPad Prism. $Chi^2$ test was used for categorical comparisons. Kruskal-Wallis test with Dunn's test for post hoc comparisons between separate groups were used for comparing all five groups, including correction for multiple comparisons.

## RESULTS

# Subjects and baseline characteristics

A total of 155 subjects were included, of which 41 were healthy never-smokers (**HNS**), 35 were never-smokers with CAL and a z-score < LLN (**$CAL_{< LLN, FEV1<100}$**), 30 were never-smokers with CAL and a z-score ≥ LLN (**$CAL_{\geq LLN, FEV1<100}$**), 26 were never-smokers with CAL and FEV1%pred. ≥ 100 (**$CAL_{FEV1\geq100}$**), and 23 were smoking controls (**SC**) with normal spirometry. The baseline characteristics for the five included groups are presented in Table 2. There were minor differences in age and height, but not weight and BMI, among the groups. More men than women were included, except for the group of smoking controls, which was dominated by women. Smoking controls displayed a higher CAT score compared

with the other four groups. A higher proportion of the subjects had asthma in the three CAL groups and the **SC** group than the **HNS** group, however, the difference was not statistically significant.

Table 2
Baseline characteristics of the study groups

| **Description** | **Healthy never-smokers** | **Never-smokers** $CAL_{< LLN, FEV1<100}$ | **Never-smokers** $CAL_{\geq LLN, FEV1<100}$ | **Never-smokers** $CAL_{FEV1\geq100}$ | **Smoking controls** | **p-value** |
|---|---|---|---|---|---|---|
| | **Normal ratio** | **Obstructive ratio** | **Obstructive ratio** | **Obstructive ratio** | **Normal ratio** | |
| | n = 41 | n = 35 | n = 30 | n = 26 | n = 23 | |
| Sex, males/females n (%) | 27/14 (66/34) | 23/12 (67/33) | 22/8 (73/27) | 18/8 (69/31) | 10/13 (38/62) | 0.22 |
| Age, years | 60 (57–62) | 57 (55–61) | 63 (59–66) | 62 (57–65) | 61 (59–64) | 0.007 |
| Height, cm | 177 (171–184) | 177 (171–183) | 183 (174–187) | 178 (173–189) | 172 (164–178) | 0.021 |
| Weight, kg | 80 (67–87) | 82 (68–88) | 86 (77–92) | 79 (75–88) | 75 (62–87) | 0.25 |
| BMI, $kg/m^2$ | 24 (22–27) | 25 (23–27) | 26 (23–29) | 25 (24–26) | 26 (22–29) | 0.56 |
| Cigarette smoking, pack-years | 0 | 0 | 0 | 0 | 20 (15–28) | n.a. |
| CAT score | 4 (1–5) | 4 (2–8) | 5 (2–8) | 4 (3–7) | 10 (5–12) | < 0.001 |
| Asthma diagnosis[a], n (%) | 2 (5%) | 6 (17%) | 7 (23%) | 8 (31%) | 6 (26%) | 0.062 |

Data is presented as median and (IQR) or otherwise stated, p-values are from $Chi^2$-test or Kruskal-Wallis test. [a] self-reported doctor's diagnosed asthma. **Abbreviations**: CAL=chronic airflow limitation (i.e. $FEV_1/FVC < 0.7$); BMI= Body Mass Index; CAT=COPD Assessment Test; LLN=Lower limit of normal.

## Post-bronchodilator dynamic and static lung volumes

The ratio and z-score of FEV1/FVC as well as FEV1% of predicted in the included study groups are presented in **Table S1.** Figure 1 shows the results of the dynamic lung volumes and confirms that values within the separate groups are below or above given limits.

Lung volumes are presented in Fig. 2, **Table S1** (%pred values and z-scores) and **Table S2** (absolute values). The group of **CAL$_{<\ LLN,\ FEV1<100}$** displayed %pred values of FVC, VC, TLC, RV and $V_A$ that did not differ significantly from **HNS**, suggesting a mild lung function deficiency with preserved lung volumes in these subjects, despite having an FEV1/FVC ratio below LLN. **CAL$_{\geq\ LLN,\ FEV1<100}$** displayed values between **CAL$_{<\ LLN,\ FEV1<100}$** and **HNS** in most cases.

In contrast to the other groups, the group of **CAL$_{FEV1\geq100}$** showed a high FVC %pred, which explains that the low FEV1/FVC ratio is due to their high values of FVC %pred. Similarly, this group showed higher % of predicted values for VC, TLC and $V_A$ compared to all other groups, which further confirms large lung volumes.

When dividing the group of subjects with large lung volumes (**CAL$_{FEV1\geq100}$**) into FEV1/FVC < or ≥ LLN (i.e. **CAL$_{<\ LLN,\ FEV1\geq100}$**, n = 9 and **CAL$_{\geq\ LLN,\ FEV1\geq100}$**, n = 17**)**, the groups with CAL < LLN and CAL ≥ LLN had similar FEV1%pred but differed in FVC %pred (p = 0.053, **Figure S1**). No further differences between these two groups were found in any of the other lung function variables, but, due to few individuals, data are further on presented only as a merged group of **CAL$_{FEV1\geq100}$**.

In conjunction with the lung volumes, the values % of predicted for both FRC and IC were higher in the group of **CAL$_{FEV1\geq100}$** compared to the group of **CAL$_{\geq\ LLN,\ FEV1<100}$** and IC was also higher compared with the group of **CAL$_{<\ LLN,\ FEV1<100}$**, which is presented in **Figure S2**.

# Post-bronchodilator diffusing capacity

The group of **CAL$_{<\ LLN,\ FEV1<100}$** did not differ in $D_{LCO}$ or $K_{CO}$ expressed as % of predicted compared to the other groups, as seen in Fig. 3. The group of **CAL$_{FEV1\geq100}$**, showed higher $D_{LCO}$ as % of predicted, compared to the group of **CAL$_{\geq\ LLN,\ FEV1<100}$** as well as to **SC**. This finding was most likely due to their larger alveolar volume, since no difference was found in $K_{CO}$ % of predicted.

# Post-bronchodilator resistance measured by body plethysmography

To further investigate the nature of airway obstruction, body plethysmography was used to assess total, inspiratory and expiratory lung resistance as showed in **Figure S3**. The group of **CAL$_{<\ LLN,\ FEV1<100}$** presented with higher both expiratory and inspiratory resistance, and subsequently also total resistance,

compared to the group of **$CAL_{FEV1\geq100}$**. Expiratory flow limitation was assessed as the difference between the expiratory and inspiratory resistance, but no difference could be seen between the included groups (**Figure S3D**).

# Post-bronchodilator resistance measured by impulse oscillometry

Airway resistance was also assessed using IOS and displayed in Fig. 4, with similar results as when determined with body plethysmography (**Figure S3)**, i.e. that the group of **$CAL_{< LLN, FEV1<100}$** displayed higher total resistance of the airways (R5) compared with the lower levels in the group of **$CAL_{FEV1\geq100}$**. Again, the group of **$CAL_{\geq LLN, FEV1<100}$** showed results in-between the group of **$CAL_{< LLN, FEV1<100}$** and **$CAL_{FEV1\geq100}$**. In addition, the latter group had the lowest level of median peripheral resistance and significantly lower than the **SC**. In addition, lower levels of reactance (X5), resonance frequency ($F_{res}$) and reactance area (AX) were seen in never-smokers with large lungs (**$CAL_{FEV1\geq100}$**) compared to **SC**. Also, **HNS** had lower peripheral resistance and reactance than **SC** (Fig. 4C, E **and F**).

IOS was also used to assess expiratory flow limitation, as a difference between inspiratory and expiratory signals separately. This was employed by calculating delta values for total, central and peripheral airway resistance, separately, as well as for reactance. Similar to the body plethysmography measurement of expiratory flow limitation, no significant differences could be found between the studied groups in any of the delta values between expiratory and inspiratory values as shown in **Figure S4**.

# Bronchodilator responsiveness results for spirometry

Pre-bronchodilator values are presented in **Table S3.** Similar pre- and post-bronchodilator results were found in the between-groups comparisons both for spirometry and IOS.

The group of **$CAL_{< LLN, FEV1<100}$** was the group with the highest proportion (26%) of subjects that were bronchodilator responsive in FEV1 (**Table S4**). All never-smoking subjects showed higher bronchodilator responsiveness as % of change from baseline in FEV1 in comparison with the **SC** (Fig. 5A), however, there were no differences in bronchodilator responsiveness in FVC among the groups (Fig. 5B).

# Bronchodilator responsiveness results for IOS

Bronchodilator responsiveness was also explored in the context of airway resistance and reactance. The group of **$CAL_{< LLN, FEV1<100}$** was found to have more bronchodilator responsiveness as % of change from baseline than the other groups, and significantly more in R5, X5, $F_{res}$ and AX compared to the **HNS** (Fig. 5C **and D**, **Figure S5** and **Table S4**).

# DISCUSSION

This study carried out a detailed mapping of the lower airway physiology in never-smokers with CAL. One main finding was that never-smokers with CAL showed a mild disease with no pronounced difference in static lung volumes compared to **HNS**, although they had increased peripheral airway resistance and related bronchodilator responsiveness.

The group of CAL with a z-score < LLN for the FEV1/FVC-ratio (**$CAL_{< LLN, FEV1<100}$**), showed a mild airway disease with similar static lung volumes as **HNS**. Nor was there any difference noted in terms of gas exchange function ($D_{LCO}$), implying that oxygenation was not affected, in line with previous data on a low prevalence of emphysema[13]. Interestingly, a difference between the groups emerged when assessing airway resistance and reactance, by using IOS. Higher airway resistance was measured in the group of **$CAL_{< LLN, FEV1<100}$** using both body plethysmography and IOS, providing evidence on a peripheral airways impact, similar to tobacco smoke-induced COPD[31, 32]. The group of **$CAL_{< LLN, FEV1<100}$** showed a more pronounced bronchodilator response than the other groups, i.e., reduced airway resistance. This is similar to the previously shown bronchodilator responsiveness on total airway resistance in smoking-induced COPD[33]. Interestingly, about a quarter of these individuals, displayed a reversibility based upon FEV1 and only 6% on FVC, a finding that differs from tobacco smoke-induced COPD[33]. This further implies that individuals in this group i.e. **$CAL_{< LLN, FEV1<100}$**, comprise a distinctive phenotype of clinical interest, as they are often detected in primary care through a low FEV1/FVC ratio. However, as conventional spirometry is not sensitive enough to detect the peripheral airway disease, impulse oscillometry is needed to define this CAL phenotype.

Here, we also included a group of never-smokers with CAL but a z-score ≥ LLN, **$CAL_{\geq LLN, FEV1<100}$**. This group showed lung function values between the two groups of **$CAL_{< LLN, FEV1<100}$** and **HNS**, suggesting an intermediate lung function stage. This gives further input to the discussion of whether the fixed ratio of FEV1/FVC (as recommended by GOLD[4]), or if FEV1/FVC < LLN (as recommended by Stanojevic et al[5]) are the most proper way to define subjects with obvious chronic airway obstruction. Consequently, from the present study, including also the results from our previous article[15], it might be suggested that the never-smokers with **$CAL_{< LLN, FEV1<100}$** have a mild COPD, while it is less likely in the group with **$CAL_{\geq LLN, FEV1<100}$**. The latter group may though be at risk for abnormal future lung function deterioration, which might also be the case for the three individuals with PRISM (Preserved ratio impaired spirometry, noted in Supplemental Table 3).

An obstructive ratio in terms of CAL can also exist due to other reasons, as observed in individuals in the group of **$CAL_{FEV1\geq100}$**, i.e. subjects with large lung volumes. It may involve younger individuals with specific physically demanding occupation or elite athletes[34–37]. Another reason could be dysanapsis, which is the concept of a disproportion between lung size and airway calibre[38]. Dysanapsis has been thought to be a normal physiological variant but has to some extent been associated with the predisposition for obstructive lung disease[5]. Thus, for those with large lung volumes, there is a physiological limit to exhale a large volume in one second, which may result in an FEV1/FVC ratio of less

than 0.7. The low FEV1/FVC ratio is in this case paradoxically a consequence of a FVC that is supranormal. It may be debated whether only individuals with **CAL$_{<\ LLN,\ FEV1\geq 100}$** clearly exhibit dysanapsis compared to individuals with **CAL$_{\geq\ LLN,\ FEV1\geq 100}$**. Nevertheless, no differences in the other lung function parameters were observed, which might suggest that the lower ratio may be primarily attributed to larger lung volumes overall. The group of **CAL$_{FEV1\geq 100}$** displayed a $D_{LCO}$ %pred that was higher than the other groups but normalized when adjusted for alveolar volume and in line with the healthy controls. Their airway resistance was low and, thus, another sign of normal lung function with large airways. Taken together, our study shows that CAL due to large lungs is a physiologically normal state, at least within this population, but it still remains unknown whether these subjects would have a different future morbidity pattern.

The common definition of COPD involves an obstructive ratio of FEV1/FVC < 0.7, as a part of the diagnosis[1]. Thus, all three groups were considered to fall within the scope of an obstructive disease. However, a key finding in our study is that the group with large lung volumes was completely healthy and that the airway obstruction in their case is a paradoxical finding. This highlights that diagnosing COPD requires more than just identifying an obstructive ratio. In contrast, this was not the case in the other two groups of CAL, where FEV1%pred was below 100.

Could the two groups with CAL, namely **CAL$_{<\ LLN,\ FEV1<100}$** and **CAL$_{\geq\ LLN,\ FEV1<100}$**, be related to something else than COPD? In all CAL groups, there was a higher prevalence of self-reported doctor's diagnosed asthma compared with the **HNS**, which may indicate either a degree of misclassification or an overlap between obstructive lung diseases. This overlap complicates the interpretation of airflow limitation based solely on spirometric criteria, particularly in populations with a high burden of respiratory symptoms. However, we have previously evaluated the impact of asthma in the same cohort, and after excluding participants with self-reported asthma, never-smokers with **CAL$_{<\ LLN,\ FEV1<100}$** still had more respiratory symptoms, worse health status and larger bronchodilator reversibility compared to **HNS**[15].

Nevertheless, our study shows that when a significant obstruction remains despite bronchodilation, COPD is suggested in the first place. Overall, our results add further weight to the argument that the group of **CAL$_{<\ LLN,\ FEV1<100}$** is a distinct phenotype with characteristics that differ from tobacco smoke-induced COPD but similarly affects the peripheral airways. This phenotype is associated with co-morbidities, such as respiratory symptoms, asthma and chronic rhinosinusitis[14–16]. This previously overlooked group of CAL and COPD in never-smokers is expected to increase in the future, and understanding lung physiology becomes even more important in order to initiate a tailored drug treatment for COPD in never-smokers, if considered feasible.

The group of smoking controls, i.e. **SC**, had a normal FEV1/FVC ratio, but the symptom assessment questionnaire indicated pathology of the lower airways. In the current study, the group of **SC** had a high tobacco load, on average 20 pack-years. Compared to **HNS**, the bronchial responsiveness as % of change from baseline of **SC**, measured as FEV1, was less pronounced. However, IOS showed increased

peripheral resistance (R5-R20), along with an impaired elastance in **SC** compared to never-smokers with CAL. Taken together, this suggests peripheral airway disease in this group, with ongoing inflammation and reduced bronchodilator responsiveness. Finally, the symptom burden was significantly higher in this group, with a median CAT score of 10 compared to 4 in the other study groups, which is at a level considered to be symptomatic COPD disease[1].

Strengths of the present study are the relatively large number of included never-smokers and that the pulmonary function tests were comprehensive and included, in addition to dynamic spirometry, static lung volumes, diffusing capacity measurement and IOS. One limitation is the narrow age span in the study. Neither did we include a group with tobacco smoke-induced COPD as a comparison, but their lung physiology in this respect is well-studied[21, 31, 32], which is not the case for the other groups included.

# CONCLUSION

This study provides further evidence that CAL in never-smokers constitutes a distinct phenotype with impact on the small airways. We have also shown that subjects with spirometrically defined CAL due to large lungs show no evidence of impaired lung physiology. Further studies are needed to investigate these groups in terms of underlying physiological mechanisms, prognosis as well as potential treatment strategies.

# Abbreviations

$D_{LCO}$
Diffusing capacity of the lungs for carbon monoxide
FEV1
Forced Expiratory Volume in one second
FRC
Function Residual Capacity
FVC
Forced Vital Capacity
GLI
Global Lung Function Initiative
GOLD
Global Initiative for Chronic Obstructive Lung Disease
IC
Inspiratory capacity
IOS
Impulse Oscillometry System
$K_{CO}$
Carbon monoxide transfer coefficient
R5

Resistance at 5 Hz
R20
Resistance at 20 Hz
R_IN
inspiratory flow resistance of the airways
R_EX
expiratory flow resistance of the airways
R_TOT
total flow resistance of the airways
RV
Residual Volume
TLC
Total Lung Capacity
$V_A$
Alveolar Volume
VC
Vital Capacity

## Declarations

# Ethics approval and consent to participate

All subjects provided written informed consent prior to inclusion in the study, which was approved by the Regional Ethical Review Board in Stockholm, Sweden (2016-841-31/12), in accordance with the Declaration of Helsinki.

**Consent for publication**

Not applicable

# Competing interest

The authors declare that they have no competing interests.

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# Author Contribution

ET and AA have made substantial contributions to the conception and design of the work, data acquisition, analysis, interpretation of data, have drafted the work and have approved the submitted version. AN, FR, JA, ABl, ABe, JSE, PKJ, CJ, AM, LP, PS, ÅW, MCS, LB have made contributions to the conception, interpretation of data, substantively revised the work and approved the submitted version.

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# Data Availability

Data cannot be shared publicly due to reasons relating to sensitive and potentially identifying participant information. The anonymized data are available from the study steering committee upon request.

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# Figures

Figure 1

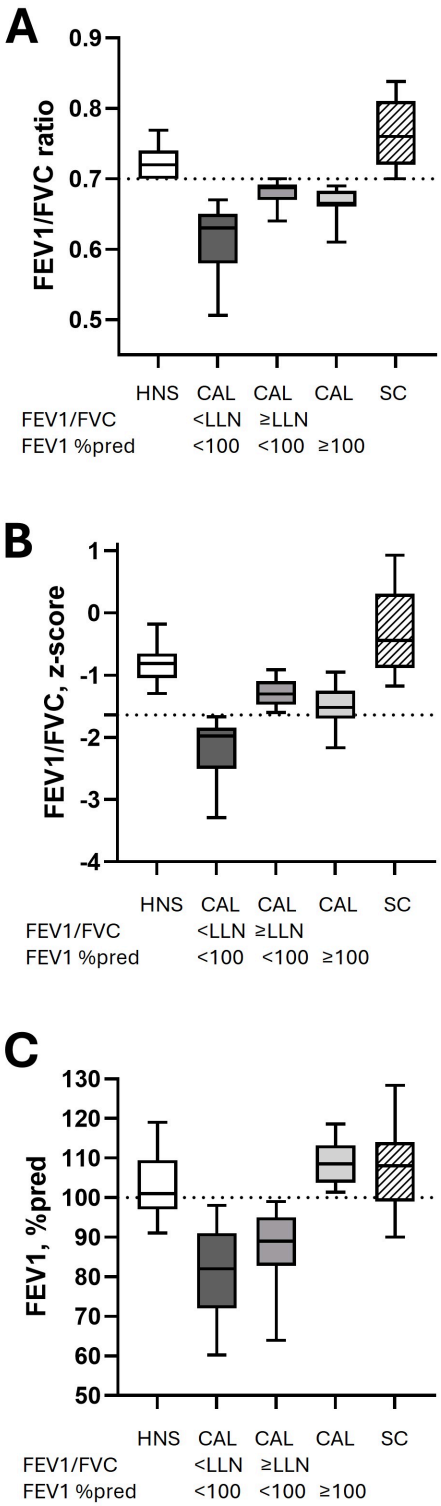



**Figure 1**

Box plots of spirometry results for Healthy never-smokers (HNS), Never-smokers with $CAL_{<LLN,\ FEV1<100}$, Never-smokers with $CAL_{\geq LLN,\ FEV1<100}$, Never-smokers with $CAL_{FEV1\geq100}$ and Smoking controls (SC). A) FEV1/FVC ratio, B) FEV1/FVC z-score and C) FEV1 % of predicted, which were used as grouping criteria. Whiskers show 5-95$^{th}$ percentile. FEV1= forced expiratory volume in 1 sec, FVC= forced vital capacity, %pred= % of predicted normal.

Figure 2

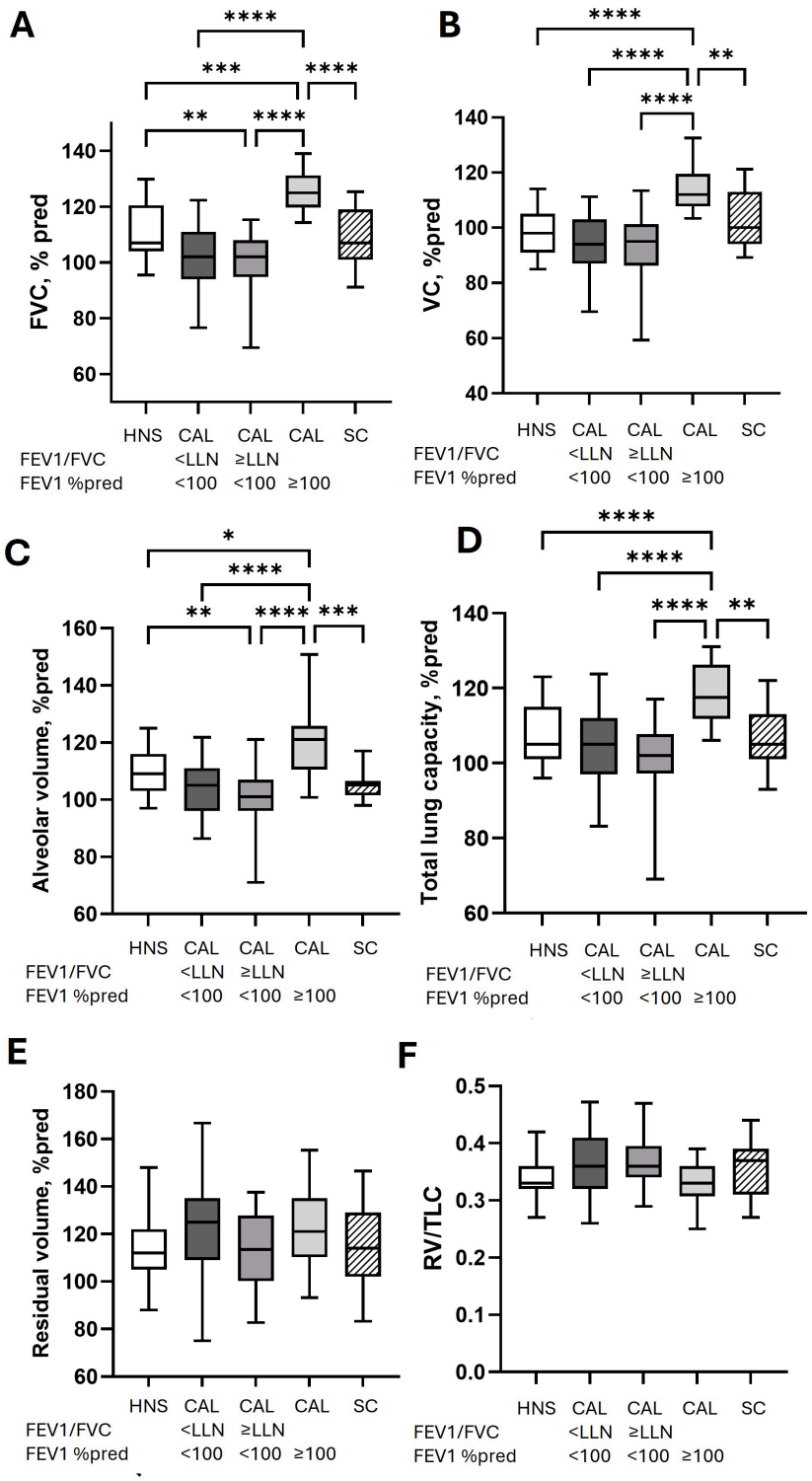



**Figure 2**

Box plots of Lung volume results for Healthy never-smokers (HNS), Never-smokers with $CAL_{<LLN, FEV1<100}$, Never-smokers with $CAL_{\geq LLN, FEV1<100}$, Never-smokers with $CAL_{FEV1\geq100}$ and Smoking controls (SC). A) FVC %pred, B) VC %pred and C) Alveolar volume %pred, D) Total lung capacity (TLC) %pred, E) Residual volume (RV) %pred and F) RV/TLC. Statistics were analysed using Kruskal-Wallis test with Dunn's post hoc test (including correction for multiple comparisons) when comparing separate groups.

Whiskers show 5-95$^{th}$ percentile, and *= <0.05, **= <0.01, ***= <0.001 and ****= <0.0001. FVC= forced vital capacity, VC=vital capacity, TLC=total lung capacity, RV=residual volume, %pred= % of predicted normal.

Figure 3

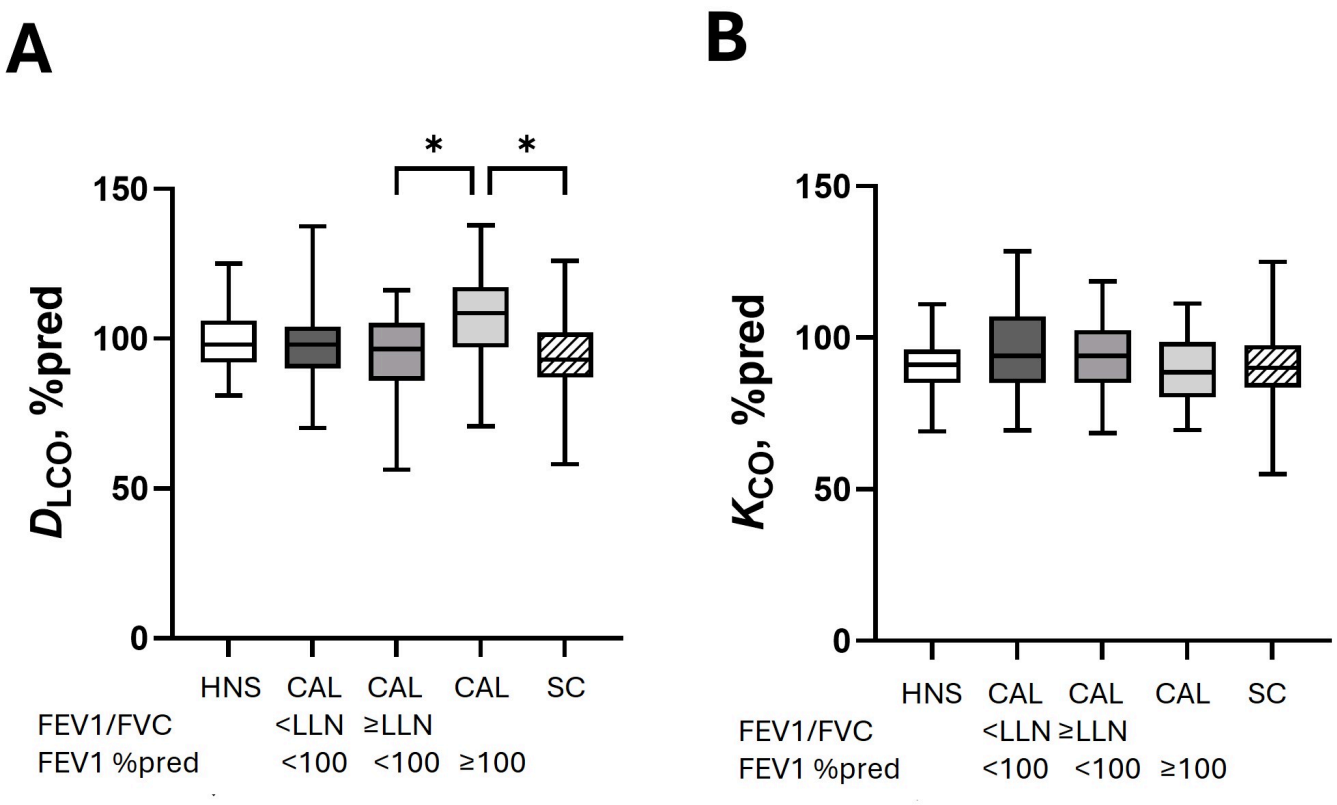



**Figure 3**

Box plots of diffusion capacity results for Healthy never-smokers (HNS), Never-smokers with $CAL_{<LLN, FEV1<100}$, Never-smokers with $CAL_{\geq LLN, FEV1<100}$, Never-smokers with $CAL_{FEV1\geq100}$ and Smoking controls (SC). A) $D_{LCO}$ %pred, B) $K_{CO}$ %pred. Statistics were analysed using Kruskal-Wallis test with Dunn's post hoc test (including correction for multiple comparisons) when comparing separate groups. Whiskers show 5-95$^{th}$ percentile, and *= <0.05. $D_{LCO}$= diffusing capacity of the lung, $K_{CO}$= Carbon monoxide transfer coefficient, %pred= % of predicted normal.

Figure 4

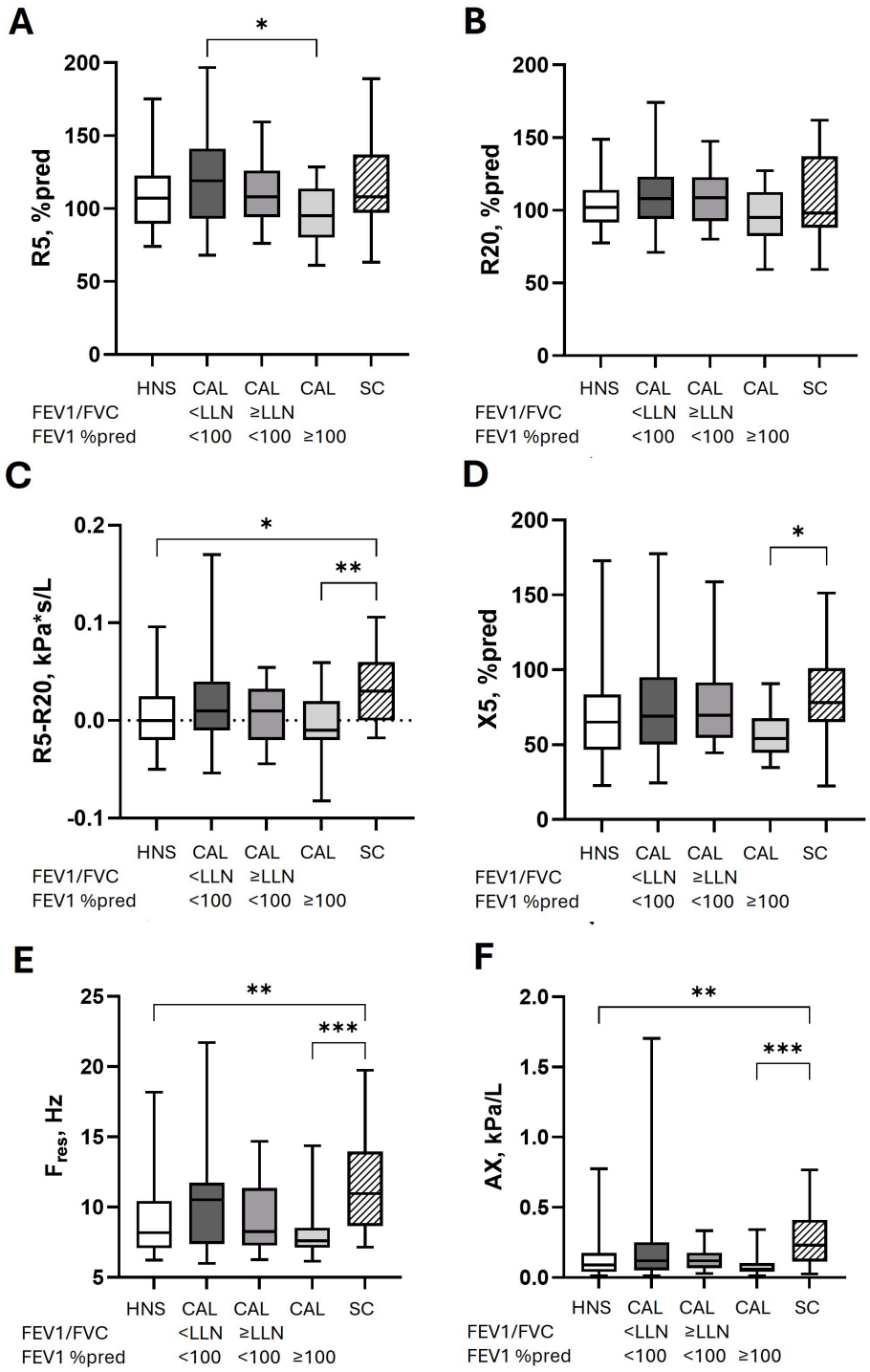



**Figure 4**

Box plots of IOS results for Healthy never-smokers (HNS), Never-smokers with $CAL_{<LLN,\ FEV1<100}$, Never-smokers with $CAL_{\geq LLN,\ FEV1<100}$, Never-smokers with $CAL_{FEV1\geq 100}$ and Smoking controls (SC). A) R5 %pred, B) R20 %pred, C) R5-R20, D) X5 %pred, E) $F_{res}$ and F) AX. Statistics were analysed using Kruskal-Wallis test with Dunn's post hoc test (including correction for multiple comparisons) when comparing

separate groups. Whiskers show 5-95$^{th}$ percentile, and *= <0.05, **= <0.01 and ***= <0.001. R5 and R20 = resistance at 5 and 20 Hz, respectively, X5=reactance at 5Hz, $F_{res}$=resonant frequency and AX=area under the reactance curve, %pred= % of predicted normal.

Figure 5

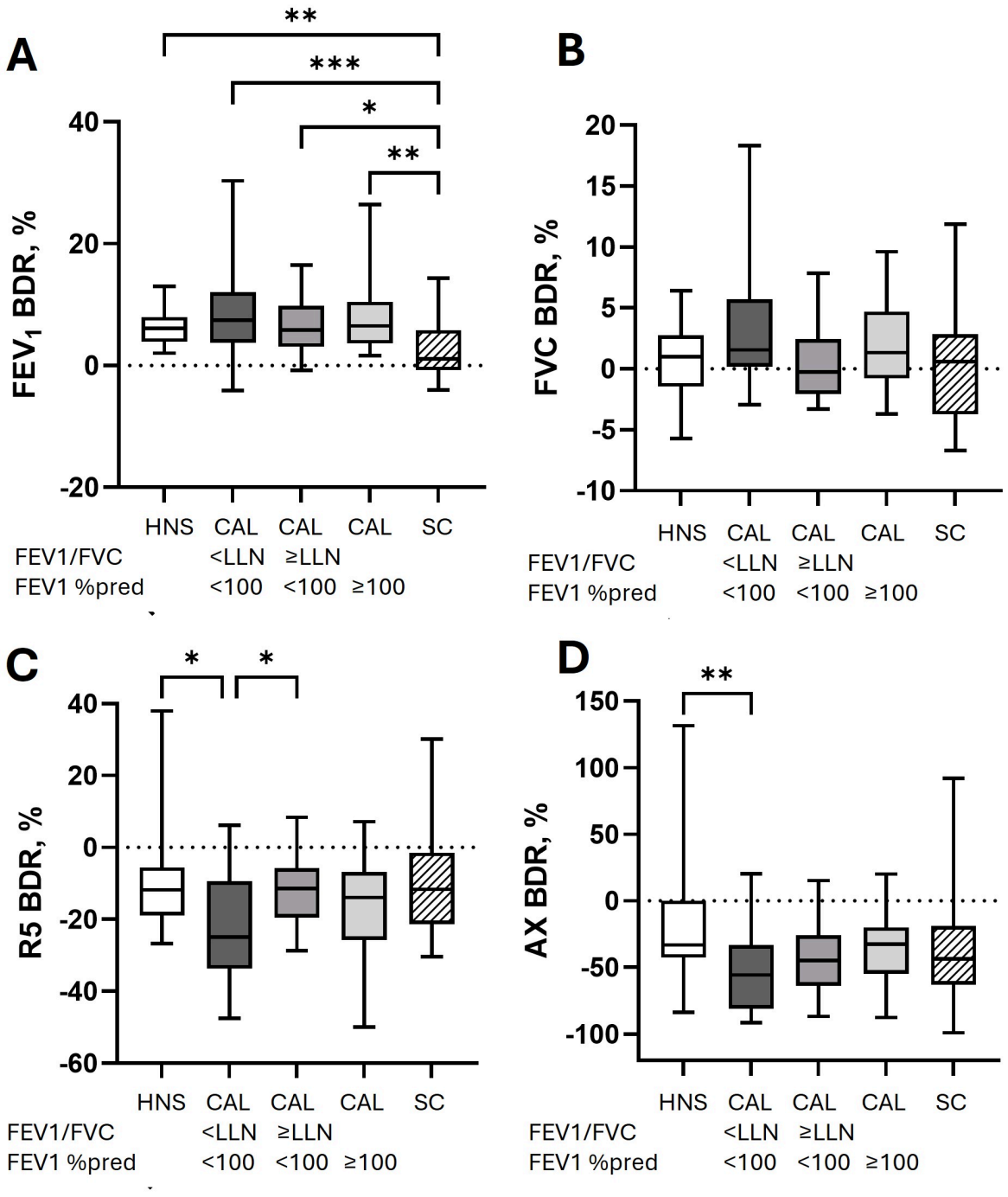



**Figure 5**

Box plots of Bronchodilator responsiveness (BDR), as % of change from baseline (pre to post) bronchodilator inhalation, in spirometry and impulse oscillometry variables for Healthy never-smokers (HNS), Never-smokers with $CAL_{<LLN,\ FEV1<100}$, Never-smokers with $CAL_{\geq LLN,\ FEV1<100}$, Never-smokers with $CAL_{FEV1\geq 100}$ and Smoking controls (SC). A) FEV1, B) FVC, C) R5 and D) AX. Statistics were analysed using Kruskal-Wallis test with Dunn's post hoc test (including correction for multiple comparisons) when comparing separate groups. Whiskers show 5-95$^{th}$ percentile, and *= <0.05, **= <0.01 and ***= <0.001. FEV1= forced expiratory volume in 1 sec, FVC= forced vital capacity, R5= resistance at 5 Hz and AX=area under the reactance curve, %pred= % of predicted normal.

## Supplementary Files

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