SUPRANORMAL LUNG FUNCTION: PREVALENCE, ASSOCIATED FACTORS AND CLINICAL MANIFESTATIONS ACROSS THE LIFESPAN

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ABSTRACT

Background and Objectives. It is now well established that there are different life-long lung function trajectories in the general population, and that some are associated with better or worse health outcomes. Yet, the prevalence, clinical characteristics and risk factors of individuals with supranormal FEV_1 or FVC values (above the upper-limit of normal (ULN) in different age-bins through the lifetime in the general population are poorly understood.

Method. To address these questions, we investigated the prevalence of supranormal FEV_1 and FVC values in the LEAD (Lung, hEart, sociAl, body) study, a general population cohort in Austria that includes participants from 6-82 years of age.

Results. We found that: *(1)* the prevalence of supranormal pre-bronchodilator FEV_1 and FVC values was 3.4% and 3.1%, respectively, and that these figures remained relatively stable through different age-bins except for participants >60 yrs., in whom they increased (5.0%, and 4.2%, respectively). Approximately 50% of supranormal individuals had both increased FEV_1 and FVC values; *(2)* supranormal spirometric values were consistently accompanied by higher static lung volumes and lower specific airway resistance through the lifespan, indicating better overall lung function; and *(3)* multivariate regression analysis identified that female sex, higher muscle mass (FFMI), less diabetes, and less respiratory symptoms were consistently associated with supranormal FEV_1 and FVC values.

Conclusions. Supranormal FEV_1 and/or FVC values occur in about 3% of the general population in different age bins and are associated with better health markers.

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INTRODUCTION

It is now well established that, in the general population, there is a range of lung function trajectories through the lifetime [1-9]. Trajectories below the normal range are associated with a higher prevalence and earlier incidence of multi-morbidity and premature death [10], whereas those above the normal range (i.e., supranormal trajectories) are associated with healthier ageing, fewer cardiovascular and respiratory events, as well as with a survival benefit [11, 12].

Many environmental, genetic, epigenetic and other host factors (e.g., prematurity or low birth weight) can influence lung function through the life time. The term GETomics has been recently proposed to illustrate the dynamic, cumulative and interactive nature of all these factors [7]. It is known that factors related to low lung function inter-relate and create a network whose complexity increases exponentially with age [13]. By contrast, however, factors associated with supranormal lung function trajectories (above their respective upper limit of normal (ULN) values for age) are largely unknown and may be different for airflow (FEV_1) and lung volume (FVC) variables [11, 12]. Here, we investigated the prevalence, associated factors and clinical characteristics of individuals with FEV_1 and/or FVC values >ULN in the LEAD study, a large and carefully characterized cohort of individuals living in Austria, randomly recruited from the general population, stratified by age (from 6 to 82 years of age), sex (male/female) and residential area (urban/rural) [14]. Specifically, we sought to: *(1)* determine the prevalence of pre-bronchodilator supra-normal values (>ULN) of FEV_1 and FVC in the general population by age bins; *(2)* investigate what factors are associated with them in these different age bins; and *(3)* describe the clinical characteristics of supranormal individuals through the lifetime.

METHODS

Study design and Ethics

The LEAD (Lung, hEart, sociAl, boDy) study (NCT01727518) is a single-centre longitudinal, observational, population-based cohort study that provides a unique comprehensive database of factors associated with lung function through the lifespan [14]. To this end, from 2012 to 2016 a random sample (stratified by age, sex, and residential area) of 11,423 subjects (47.6% males) aged 6-82 years from Vienna and lower rural Austria was investigated. The Vienna Ethics Committee approved the study (EK-11-117-0711). All participants signed informed consent; in those younger than 18 years, it was signed by their parents or legal representatives.

Measurements

The methodology of LEAD has been detailed elsewhere [14] and is only summarized here (see Table S1 for detailed information on variables included in the current study). In brief, the following measurements were obtained in all participants at recruitment in the Ludwig Boltzmann Institute for Lung Health at the Clinic Penzing in Vienna (Austria), following standard operation procedures [14]: *(1)* demographics (age, sex), anthropometrics (height, and weight) and socioeconomic status (SES) [15]; *(2)* smoking status (never, former, current), cumulative smoking exposure (pack years) and other exposures, including second-hand smoking, air pollution, nitrogen dioxide levels (NO_2) and particular matter (PM10) levels near home; *(3)* blood pressure and electrocardiogram; *(4)* skin prick test; *(5)* spirometry and body plethysmography (BT-MasterScope Body 0478, Jaeger, Germany) following international guidelines [16]. Reference values were those of the Global Lung function Initiative (GLI) [17, 18]; *(6)* comorbidities and medication; *(7)* body composition (fat and fat free body mass) was estimated with a Lunar Prodigy™ DXA (dual x-ray absorptiometry) scan (GE Healthcare, USA) using enCORE™ v17; and, finally, *(8)* a fasting venous blood sample was obtained by peripheral venipuncture for standard biochemistry and total and differential cell counts using a certified laboratory.

Data analysis

Figure 1 presents the consort diagram of the study. The LEAD cohort originally recruited 11,423 subjects. For the current analysis we excluded those with invalid spirometry (n=196) and those with pre-bronchodilator FEV_1 or FVC < lower limit of normal (LLN; n=1,205) according GLI equations [17]. The remaining participants (n=10,222) were stratified into two mutually exclusive categories according to the ULN (z-score>1.645) of FEV_1 or FVC values: *(1) Normal* when the FEV_1 (or FVC values) were between LLN and ULN; or *(2) Supranormal* when FEV_1 (or FVC) were higher than ULN. Normal and supranormal participants so defined were compared in the entire study population and by age bins (6 to <20, 20 to <40, 40 to <60 and ≥60 years of age).

Results are presented as total counts and % or mean ± standard deviation. Differences between normal and supranormal participants were compared using the Welch t-test or Chi-square (Fisher's Exact) test for continuous and categorical variables, respectively, and p-values were adjusted for multiple comparisons using the False Discovery Rate (FDR) method [19]. Because the sample size of the supranormal population was much lower than the normal one, to validate the observations made in the entire population we conducted a case-control analysis in supra-normal individuals *vs.* the same number of normal participants (n = 383 for FEV_1 and n = 351 for FVC) matched individually for sex and age (R version 4.1.2). We used multiple logistic regression analysis to identify variables independently associated with supranormal FEV_1 and FVC values in the entire study population, where we included all variables shown in Table 1 (selected from previous literature and clinical expertise) with <20% missing values. Results are shown as odds ratios (OR) and 95% confidence intervals [95% CI]. Finally, we used network analyses to depict bivariate correlations (Spearman's Rho) among variables identified in the multiple logistic regression analysis using Cytoscape (http://cytoscape.org). All analyses were performed with SPSS version 27 (IBM Corp., VA, NY).

RESULTS

Prevalence of supranormal pre-bronchodilator FEV$_1$ and FVC values

The prevalence of supranormal pre-BD FEV$_1$ and FVC values in the entire study population with valid spirometry (n=11,227) was 3.4%, and 3.1%, respectively. It was similar across age bins, except for individuals older than 60 years of age in whom supranormal FEV1 and FVC were significantly higher compared to all other age bins (Figure 2A). About 50% of supra-normal individuals had both supranormal pre-BD FEV$_1$ and supranormal FVC values (Figure 2B). Finally, 247 participants (2.4%) showed FEV1/FVC ratio > ULN; among them, 16 participants (6.5%) had a concomitant supranormal FEV1 and none a supranormal FVC value.

Supranormal FEV$_1$ values

Participants with supranormal pre-BD FEV$_1$ values were slightly older, shorter, thinner, and more often female (Table 1). By design, their spirometric values were higher but, of note, their total lung capacity (TLC), residual volume (RV) and functional residual capacity (FRC) were also higher, whereas their specific airway resistance (sReff) was lower. Supranormal individuals reported less respiratory symptoms, particularly wheezing, and had less cumulative exposure to tobacco smoking (pack-years). There were no significant differences in other environmental exposures, lifestyle, early life events or family history, but their personal past-history included less atopy (prick test) and asthma as well as reduced circulating eosinophil levels. Osteopenia/osteoporosis was slightly more frequent in supranormal individuals. Case-control analysis (Table 1) confirmed that supranormal individuals continue to be shorter, had better lung function, and reported less wheezing, asthma and smoking exposure.

Figure 3A presents the results of the multivariate regression analysis for supranormal FEV_1 values in the entire study population. The presence of diabetes, wheezing, a diagnosis of asthma ever, a high Body Mass Index (BMI) and cumulative smoking exposure (pack years) were the factors clearly associated with a reduced likelihood of supranormal FEV_1 values, whereas increased age, female sex and high Fat Free Mass Index (FFMI) were clearly associated with increased OR of supranormal FEV_1 values. The other variables selected by the model had either a smaller effect or did not reach the threshold ($p<0.05$) for statistical significance but contributed independently to the identification of supra-normals. Figure 4 (left panel) presents a correlation network (Spearman's Rho) between the factors identified by multiple regression in relation to FEV_1>ULN. Most of them, but not wheezing, were related by either positive (continuous lines) or negative (dashed lines) bivariate relationships.

Finally, Table S2 presents results by age-bins. Supranormal individuals tended to be shorter, and lighter (lower BMI), particularly above 40 years of age. Lung function parameters were consistently and significantly higher in supranormal through the life span. Respiratory symptoms, particularly wheezing, was generally reduced in supranormal individuals, who also smoked less in adulthood (40-60 years). The prevalence of osteopenia/ osteoporosis was higher in supranormal individuals above 60 years of age, and inflammatory biomarkers including hsCRP and eosinophils, were significantly lower during adulthood and in the elderly, respectively.

Supra-normal FVC values

Individuals with supranormal FVC values were slightly older and had a lower Fat Mass Index (FMI) and higher FFMI (Table 2). By design, they had higher spirometric values, but static lung volumes were higher too. They tend to report respiratory symptoms less often reported, but differences did not reach statistical significance. They live more frequently in a rural environment and were slightly less often breast fed. Diabetes was significantly less prevalent and they showed reduced circulating levels of eosinophils and hsCRP. Case-control results confirmed differences in FMI, FFMI, lung function, diabetes prevalence, and eosinophil and hsCRP levels (Table 2).

Figure 3B shows that diabetes, dyspnea, high BMI and high hsCRP were significantly associated with a reduced OR for supranormal FVC values, whereas higher FFMI and female sex were associated with the highest OR. Other variables selected by the multivariate logistic regression model had a smaller effect or did not achieve statistical significance ($p<0.05$) but contributed independently to the identification of supranormals (Figure 3B). Figure 4 (right panel) shows that most of these factors, but not dyspnea or diabetes, were related (positively or negatively).

Finally, Table S3 compares these variables by age bins. Anthropometric (sex, height, and weight) and body composition measurements (BMI, FMI, FFMI) tended to remain as seen in the entire population, reaching statistical significances in adults (20-40 years, 40-

60 years), and elderly (60+) participants. Lung function remained higher through life while other variables were more variable over time (Table S3).

DISCUSSION

The main observations of this study are that: *(1)* the prevalence of supranormal pre-bronchodilator (BD) FEV_1 and FVC values was 3.4% and 3.1%, respectively, in the LEAD cohort, that these figures remained relatively stable through life except for participants >60 yrs., in whom they increased (5.0%, and 4.2%, respectively), and that about 50% of supranormal individuals had both increased FEV_1 and FVC values; *(2)* supranormal spirometric values were consistently accompanied by higher static lung volumes and lower specific airway resistance through the lifetime, indicating that these spirometric changes truly reflect better lung function; and, *(3)* multivariate regression analysis identified several factors associated with supranormal spirometric values, most notably female sex, higher muscle mass (FFMI) and lower BMI, less diabetes, and less respiratory symptoms, indicating that supranormal FEV_1 and/or FVC values are associated with better health markers through the life span [20, 21].

Previous studies

It is now well established that there is a range of lung function trajectories through the lifetime and that trajectories below the normal range are associated with poorer health outcomes [1-9]. Supranormal trajectories are less well studied. Çolak *et al* recently reported that the prevalence of supranormal (>ULN) pre-BD FEV_1 and FVC in the general population aged 40-60 years in the Copenhagen General Population Study were 3.6% and 5.5%, respectively [11, 12]. These figures are slightly higher than our observations here in these same age range (2.9% and 3.9%, Figure 2, panel A). Of note, Çolak *et al* also reported that supranormal FEV_1 and FVC values were associated with better health outcomes, including COPD incidence, cardiovascular events, hospitalizations, and death during follow-up [11, 12]. Our results extend these previous observations by investigating the prevalence, associated factors and clinical presentation of supranormal spirometric values across the lifespan (from childhood to elderly) and by age bins using a much more detailed phenotypic characterization, including the measurements of static lung volumes and airway resistance by plethysmography, body composition by DXA-scanning and the quantification of several circulatory inflammatory markers.

Interpretation of novel observations

The prevalence of supranormal lung function values (around 3% in this study) is about half of that seen for values below the LLN (around 8%) in the same LEAD cohort [13], suggesting that, as discussed explicitly below, factors limiting lung growth are more prevalent and/or potent that those favoring it. On the other hand, we observed that the prevalence of supranormal pre-BD spirometric values did not change very much in different age bins through the lifespan, except at older ages, where they increase (Figure 2A). This may relate to the fact that supranormal individuals live longer [11, 12], so there may be a survival effect.

For the first time in this setting, we used body plethysmography to determine static lung volumes and airway resistance. We found that supranormal spirometric values were invariably accompanied by higher static lung volumes and lower specific airway resistance through the lifetime, indicating that supranormal spirometric values truly identify a subpopulation of individuals with better lung function, which in turn can contribute to their longer longevity and healthier ageing [11, 12]. In keeping with these physiologic observations, we also observed that the prevalence of respiratory symptoms was lower in supranormal individuals in different age bins.

Our study identified several factors associated with supranormal spirometric values which were often shared between FEV_1 and FVC. The two most clearly associated with supranormal FEV_1 and FVC values were female sex and higher muscle mass (FFMI), whereas the presence of diabetes and respiratory symptoms were clearly associated with a reduced OR of displaying supranormal spirometric values (Figure 3, panels A and B). The precise biologic mechanisms underlying these observations cannot be inferred from our observations in this epidemiological study, but we can speculate on some of them. First, female sex was clearly associated to supranormal FEV_1 and FVC values through the life span. This suggests that female sex hormones may favor lung development [22, 23]. Second, a higher FFMI (and to some extend reduced FMI and BMI) were also clearly associated with supranormal FEV_1 and FVC values.. In this setting, it is of note that we have previously reported that lower FFMI is associated with reduced lung function in the LEAD cohort [24]. That participants with supranormal spirometric value had less respiratory symptoms seems quite straightforward. What is both surprising and interesting, though, is the strong association between the presence of diabetes and a reduced OR of supranormal values (Figure 3). Of note, too, we have reported previously a higher prevalence of diabetes in young adults with low lung function [10], suggesting still poorly understood links between carbohydrate metabolism and lung function [25].

We also identified other factors associated with a higher or lower OR of supranormal spirometric values, including height, smoking exposure, age, breastfeeding, living near a main road or osteopenia among others (Figure 3, panel A and B), although some of them did not achieve statistical significance. Of note, many of these factors were related among themselves (Figure 4) but some of them not, suggesting that for some factors there might be an additive effect, while for others as wheezing not.

Finally, it is remarkable that only a few environmental factors (e.g., tobacco smoking) are related to supranormal lung function (Figure 3). This suggests that genetic, epigenetic and/or host factors are likely more relevant in this context [7]. Yet, it is important to note that our analysis here compares supranormal to normal individuals, not to participants with reduced lung function, supporting that the absence of risk factor(s) for low lung function might not necessarily result in supranormal values. In fact, given that the OR values of the factors significantly related to supranormal lung function trajectories are relatively small (Figure 3), it may be necessary that several of these factors coexist in the same individual to drive lung function above normal.

Strengths and limitations

The strengths of our study are that it investigates supranormal spirometric values in a large, contemporary [26], general population cohort, both in the entire study population and by age bins. Likewise, it includes in the analysis several variables not usually measured in epidemiologic studies (e.g., lung volumes, airway resistance, body composition, diabetes and pre-diabetes, and systemic inflammation). We acknowledge, however, several potential limitations. First, the fact that we excluded from the multiple logistic regression analysis variables with >20% missing values may introduce potential selection bias. Yet we do not think this is the case because we excluded only one variable because of this criteria (income, 25% missing values). Second, the age bins analyzed here cover roughly periods of 20 years of age. Yet, the 6–20-year bin includes children, adolescents, and young adults, all of them with different lung developmental phases. A more fragmented analysis of this bin separating children, adolescents and young adults is not possible because of the small number of participants with values above the ULN (Table S2/S3). This may need to be addressed in larger future studies focused on this lung growth phase. Third, the fact that this is an observational study does not allow us to dive deeply into the specific biologic mechanisms underlying our observations, although we speculate on some of them above. Finally, the fact that it is a cross-sectional analysis (in different age bins) and not a longitudinal study of lung function trajectories limit our capacity to explore the relation of our findings with clinically relevant outcomes over time. However, the LEAD cohort is being followed-up regularly, so we plan to explore these relationships in future analysis.

Conclusions

Supranormal lung function values occur in around 3% of the general population through the lifetime and are more significantly associated with female sex, more muscle mass, less respiratory symptoms, and less diabetes.

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AUTHORSHIP AND CONTRIBUTORSHIP

Contributions to conception and design: CS, RF, MKB, OB, SH, AA, RBK; Data analysis: CS, AO, TM, PP, RF, AA; Interpretation of data: CS, RF, AA, RBK; Drafting the article or revising it critically for important intellectual content: All authors; Gave final approval of the version to be published: All authors; Take responsibility for the integrity of the data and accuracy of the data analysis: All authors

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TABLES

Table 1. Comparison of participants with normal and supranormal pre-BD FEV$_1$ in the entire study population. For further explanation, see text.

FEV$_1$		**Supranormal (n=383)**		**Normal total population (n=9839)**		**p-value**	**Normal case-control (n=383)**	**p-value**
Demographics and body composition		n		n				
Age (years)	Mean ± SD	383	49.0 ±21.1	9839	44.5 ±19.3	**<0.001**	49.0 ±20.4	1.000
Male, n (%)	Male	383	156 (40.7)	9839	4647 (47.2)	**0.037**	156 (40.7)	1.000
Height (cm)	Mean ± SD	383	164.4 ±13.0	9839	168.2 ±12.5	**<0.001**	167.2 ±12.3	**0.009**
Weight (kg)	Mean ± SD	383	69.2 ±17.5	9839	72.2 ±18.7	**0.003**	71.4 ±17.6	0.179
BMI, kg/m^2	Mean ± SD	383	25.2 ±4.6	9839	25.2 ±5.1	0.982	25.3 ±5.0	0.903
FMI, kg/m^2	Mean ± SD	376	8.3 ±3.3	9572	8.5 ±3.7	0.189	8.9 ±3.6	0.05
FFMI, kg/m^2	Mean ± SD	376	17.0 ±2.5	9572	16.7 ±2.6	0.144	16.5 ±2.4	**0.041**
Lung function								
FEV$_1$ pre, % pred. GLI	Mean ± SD	383	127.9 ±6.7	9839	98.9 ±10.3	**<0.001**	99.4 ±10.7	**<0.001**
FVC pre, % pred. GLI	Mean ± SD	383	124.1 ±9.5	9839	100.5 ±10.3	**<0.001**	100.6 ±10.7	**<0.001**
FEV$_1$/FVC pre (%)	Mean ± SD	383	83.1 ±6.0	9839	79.8 ±7.0	**<0.001**	79.6 ±7.3	**<0.001**
TLC % predicted (GLI)	Mean ± SD	383	122.9 ±11.2	9839	106.4 ±10.7	**<0.001**	107.1 ±10.9	**<0.001**
RV % predicted (GLI)	Mean ± SD	383	134.0 ±26.9	9839	129.7 ±26.2	**0.006**	129.9 ±25.1	0.081
FRC % predicted (GLI)	Mean ± SD	383	123.9 ±20.7	9839	109.6 ±18.9	**<0.001**	111.5 ±19.0	**<0.001**
Specific airway resistance (sR$_{eff}$) pre, kPa/s	Mean ± SD	383	0.8 ±0.3	9839	0.9 ±0.3	**<0.001**	0.9 ±0.3	**<0.001**
Symptoms								
Coughing, n (%)	Yes	383	37 (9.7)	9839	1245 (12.7)	0.159	54 (14.1)	0.166
Sputum, n (%)	Yes	383	28 (7.3)	9839	963 (9.8)	0.189	42 (11.0)	0.202
Wheezing, n (%)	Yes	383	11 (2.9)	9839	856 (8.7)	**<0.001**	35 (9.1)	**<0.001**

Table 1 cont. Comparison of participants with normal and supranormal pre-BD FEV_1 in the entire study population.

Dyspnea, n (%)	Yes	383	6 (1.6)	9839	297 (3.0)	0.194	17 (4.4)	0.084
Exposures								
Smoking Status, n (%)	Never	383	204 (53.3)	9836	4952 (50.3)	0.078	195 (50.9)	0.139
	Former		119 (31.1)		2807 (28.5)		103 (26.9)	
	Current		60 (15.7)		2077 (21.1)		85 (22.2)	
Pack years	Mean ± SD	381	5.7 ±12.0	9808	8.4 ±16.7	**<0.001**	10.1 ±18.3	**<0.001**
Secondhand smoking, ever, n (%)	Yes	383	211 (55.1)	9823	5508 (56.1)	0.777	220 (57.6)	0.714
Air pollution, n (%)	Low	383	222 (58.0)	9839	5138 (52.2)	0.073	214 (55.9)	0.754
Living on or near main road, n (%)	None	378	137 (36.2)	9717	3891 (40.0)	0.213	141 (37.8)	0.839
Lifestyle								
Rural Residence, n (%)	Rural	383	77 (20.1)	9839	1571 (16.0)	0.079	68 (17.8)	0.657
Physical activity >60min/day n (%)	Yes	383	212 (55.4)	9837	4960 (50.4)	0.124	198 (51.7)	0.508
SES, n (%)	Low	383	22 (5.7)	9835	747 (7.6)	0.357	20 (5.2)	0.486
	Medium		221 (57.7)		5364 (54.5)		241 (63.1)	
	High		140 (36.6)		3724 (37.9)		121 (31.7)	
Education, n (%)	Low	383	117 (30.5)	9816	2765 (28.2)	0.398	123 (32.2)	0.818
Income, n (%)	Low	300	38 (12.7)	7416	1058 (14.3)	0.546	35 (12.1)	1.000
Occupation, n (%)	Low	383	77 (20.1)	9834	2441 (24.8)	0.084	73 (19.1)	0.903
Early life events								
No breastfeeding	Yes	383	86 (22.5)	9839	2084 (21.2)	0.638	70 (18.3)	0.329
Hospitalization age <5, n (%)	Yes	378	16 (4.2)	9593	536 (5.6)	0.374	21 (5.6)	0.677
Family history								
Parental Allergy, n (%)	Yes	383	57 (14.9)	9839	1832 (18.6)	0.136	51 (13.3)	0.754
Parental Asthma/COPD, n (%)	Yes	383	44 (11.5)	9839	1153 (11.7)	0.976	50 (13.1)	0.754
Comorbidities								

Table 1 cont. Comparison of participants with normal and supranormal pre-BD FEV_1 in the entire study population.

Positive skin prick, n (%)	Yes	379	116 (30.6)	9722	3657 (37.6)	**0.019**	116 (30.8)	1.000
Asthma, ever, n (%)	Yes	383	13 (3.4)	9839	797 (8.1)	**0.003**	34 (8.9)	**0.011**
Allergy, ever n (%)	Yes	383	117 (30.5)	9839	3512 (35.7)	0.086	115 (30.0)	1.000
COPD, ever, n (%)	Yes	383	8 (2.1)	9839	370 (3.8)	0.185	25 (6.5)	**0.013**
Diabetes, diagnosed, n (%)	Yes	383	9 (2.3)	9839	413 (4.2)	0.159	23 (6.0)	0.053
Osteopenia/osteoporosis, n (%)	Normal	374	175 (46.8)	9491	5160 (54.4)	**0.037**	188 (50.8)	0.358
	Osteopenia		165 (44.1)		3630 (38.2)		160 (43.2)	
	Osteoporosis		34 (9.1)		701 (7.4)		22 (5.9)	
Circulating inflammatory biomarkers								
Eosinophils, g/L	Mean ± SD	371	0.1 ±0.1	9535	0.2 ±0.1	**0.018**	0.2 ±0.1	0.508
Neutrophils x10^3 cells/uL	Mean ± SD	371	3.9 ±1.5	9543	3.9 ±1.5	0.313	4.0 ±1.5	0.186
Fibrinogen, g/L	Mean ± SD	366	3.1 ±0.7	9306	3.1±0.7	0.315	3.2 ±0.7	**0.013**
hsCRP, mg/L	Mean ± SD	375	1.7 ±6.5	9510	2.0 ±4.1	0.357	2.2 ±4.5	0.357

BMI: body mass index; FMI: fat mass index; FFMI: fat free mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; SES: socioeconomic status; COPD: chronic obstructive pulmonary disease; hsCRP: high-sensitivity C-reactive protein.

Table 2. Comparison of participants with normal and supranormal pre-BD FVC in the entire study population. For further explanation, see text.

FVC		**Supranormal (n=351)**		**Normal total population (n=9871)**		**p-value***	**Normal Case-control (n=351)**	**p-value***
Demographics and body composition		n		n				
Age (years)	Mean ± SD	351	48.2 ±19.2	9871	44.5 ±19.4	**0.004**	48.0 ±19.6	1.000
Male, n (%)	Male	351	148 (42.2)	9871	4655 (47.2)	0.116	148 (42.2)	1.000
Height (cm)	Mean ± SD	351	166.8 ±12.1	9871	168.1 ±12.5	0.098	166.9 ±12.4	1.000
Weight (kg)	Mean ± SD	351	70.3 ±15.8	9871	72.1 ±18.8	0.096	71.1 ±17.6	0.705
BMI, kg/m^2	Mean ± SD	351	25.0 ±4.0	9871	25.2 ±5.2	0.411	25.2 ±4.8	0.632
FMI, kg/m^2	Mean ± SD	343	7.9 ±3.0	9605	8.5 ±3.7	**<0.001**	8.8 ±3.6	**0.005**
FFMI, kg/m^2	Mean ± SD	343	17.1 ±2.4	9605	16.7 ±2.6	**0.017**	16.5 ±2.5	**0.013**
Lung function								
FEV_1 pre, % pred. GLI	Mean ± SD	351	123.1 ±10.6	9871	99.1 ±10.8	**<0.001**	99.3 ±11.2	**0.002**
FVC pre, % pred. GLI	Mean ± SD	351	128.9 ±7.0	9871	100.5 ±10.0	**<0.001**	100.5 ±10.8	**0.002**
FEV_1/FVC pre (%)	Mean ± SD	351	76.8 ±6.2	9871	80.0 ±7.0	**<0.001**	79.6 ±7.1	**0.002**
TLC % predicted (GLI)	Mean ± SD	351	127.1 ±8.9	9871	106.3 ±10.5	**<0.001**	106.9 ±11.1	**0.002**
RV % predicted (GLI)	Mean ± SD	351	136.6 ±24.3	9871	129.6 ±26.3	**<0.001**	130.9 ±26.8	**0.011**
FRC % predicted (GLI)	Mean ± SD	351	128.8 ±19.8	9871	109.5 ±18.8	**<0.001**	110.7 ±18.6	**0.002**
Specific airway resistance (sReff) pre, kPa/s	Mean ± SD	351	0.8 ±0.3	9871	0.9 ±0.3	0.411	0.9 ±0.3	0.394
Symptoms								
Coughing, n (%)	Yes	351	40 (11.4)	9871	1242 (12.6)	0.616	61 (17.4)	0.086
Sputum, n (%)	Yes	351	38 (10.8)	9871	953 (9.7)	0.616	46 (13.1)	0.611
Wheezing, n (%)	Yes	351	20 (5.7)	9871	847 (8.6)	0.115	38 (10.8)	0.063
Dyspnea, n (%)	Yes	351	3 (0.9)	9871	300 (3.0)	0.067	11 (3.1)	0.132

Table 2 cont. Comparison of participants with normal and supranormal pre-BD FVC in the entire study population.

Exposures								
Smoking Status, n (%)	Never	351	165 (47.0)	9868	4991 (50.6)	0.096	170 (48.6)	0.517
	Former		121 (34.5)		2805 (28.4)		104 (29.7)	
	Current		65 (18.5)		2072 (21.0)		76 (21.7)	
Pack years	Mean ± SD	349	7.4 ±14.5	9840	8.4 ±16.7	0.364	9.5 ±16.6	0.151
Secondhand smoking, ever, n (%)	Yes	351	204 (58.1)	9855	5515 (56.0)	0.55	213 (60.7)	0.705
Air pollution, n (%)	Low	351	202 (57.5)	9871	5158 (52.3)	0.103	185 (52.7)	0.394
Living on or near main road, n (%)	None	347	121 (34.9)	9748	3907 (40.1)	0.103	149 (43.1)	0.086
Lifestyle								
Rural Residence, n (%)	Rural	351	75 (21.4)	9871	1573 (15.9)	**0.024**	54 (15.4)	0.122
Physical activity >60min/day n (%)	Yes	351	196 (55.8)	9869	4976 (50.4)	0.098	190 (54.1)	0.845
SES, n (%)	Low	351	20 (5.7)	9867	749 (7.6)	0.487	16 (4.6)	0.611
	Medium		192 (54.7)		5393 (54.7)		209 (59.5)	
	High		139 (39.6)		3725 (37.8)		126 (35.9)	
Education, n (%)	Low	350	101 (28.9)	9849	2781 (28.2)	0.885	91 (26.0)	0.632
Income, n (%)	Low	281	36 (12.8)	7435	1060 (14.3)	0.616	36 (12.9)	1.000
Occupation, n (%)	Low	351	77 (21.9)	9866	2441 (24.7)	0.365	71 (20.2)	0.818
Early life events								
No breastfeeding	Yes	351	94 (26.8)	9871	2076 (21.0)	**0.034**	72 (20.5)	0.132
Hospitalization age <5, n (%)	Yes	346	9 (2.6)	9625	543 (5.6)	0.058	22 (6.3)	0.085
Family history								
Parental Allergy, n (%)	Yes	351	62 (17.7)	9871	1827 (18.5)	0.792	63 (17.9)	1.000
Parental Asthma/COPD, n (%)	Yes	351	37 (10.5)	9871	1160 (11.8)	0.616	41 (11.7)	0.845
Comorbidities								
Positive skin prick, n (%)	Yes	348	117 (33.6)	9753	3656 (37.5)	0.241	117 (33.8)	1.000
Asthma, ever, n (%)	Yes	351	29 (8.3)	9871	781 (7.9)	0.909	26 (7.4)	0.893

Table 2 cont. Comparison of participants with normal and supranormal pre-BD FVC in the entire study population.

Allergy, ever n (%)	Yes	351	126 (35.9)	9871	3503 (35.5)	0.92	112 (31.9)	0.486
COPD, ever, n (%)	Yes	351	6 (1.7)	9871	372 (3.8)	0.104	13 (3.7)	0.306
Diabetes, diagnosed, n (%)	Yes	351	3 (0.9)	9871	419 (4.2)	**0.011**	18 (5.1)	**0.009**
Osteopenia/osteoporosis, n (%)	Normal	343	163 (47.5)	9522	5172 (54.3)	0.096	153 (44.3)	0.845
	Osteopenia		150 (43.7)		3645 (38.3)		159 (46.1)	
	Osteoporosis		30 (8.7)		705 (7.4)		33 (9.6)	
Circulating inflammatory biomarkers								
Eosinophils, g/L	Mean ± SD	345	0.1 ±0.1	9561	0.2 ±0.1	**0.004**	0.2 ±0.1	**0.013**
Neutrophils x10^3 cells/uL	Mean ± SD	345	3.8 ±1.5	9569	3.9 ±1.5	0.098	4.0 ±1.5	0.122
Fibrinogen, g/L	Mean ± SD	337	3.1 ±0.7	9335	3.1 ±0.7	0.399	3.2 ±0.7	**0.011**
hsCRP, mg/L	Mean ± SD	346	1.3 ±1.8	9539	2.0 ±4.3	**<0.001**	2.0 ±2.7	**0.002**

BMI: body mass index; FMI: fat mass index; FFMI: fat free mass index; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; SES: socioeconomic status; COPD: chronic obstructive pulmonary disease; hsCRP: high-sensitivity C-reactive protein.

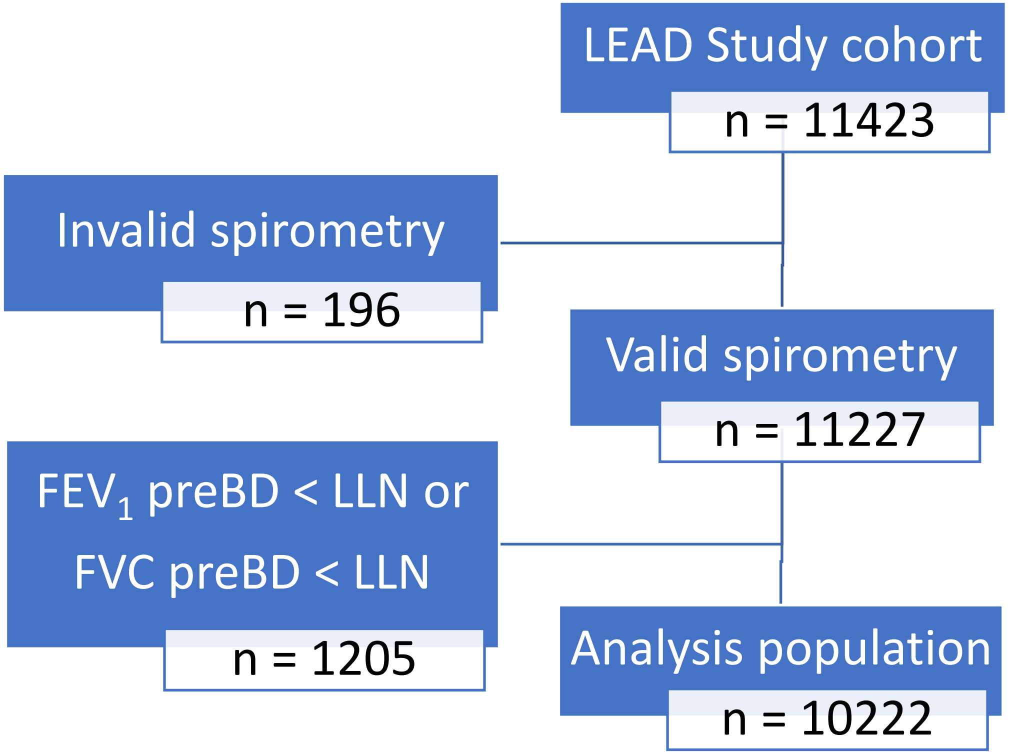
FIGURE LEGENDS

Figure 1. Consort diagram of the study. LLN: lower limit of normal.

Figure 2. *Panel A.* Prevalence (total and by age bins) of supranormal (>ULN) pre-BD FEV_1 or FVC values in the LEAD cohort (n = 11,227 subjects with valid spirometry at recruitment). *Panel B.* Prevalence of isolated supranormal pre-BD FEV_1 (blue left oval) or pre-BD FVC values (green right oval) in this population. The intersection area of this Venn diagram illustrates the prevalence of coexisting supranormal pre-BD FEV_1 *and* FVC values in the same individual (which occurred in about half of the total number of cases studied). [#] indicates significant increase in females gender vs normal population. BD: bronchodilation; ULN: upper limit of normal. For further explanations, see text.

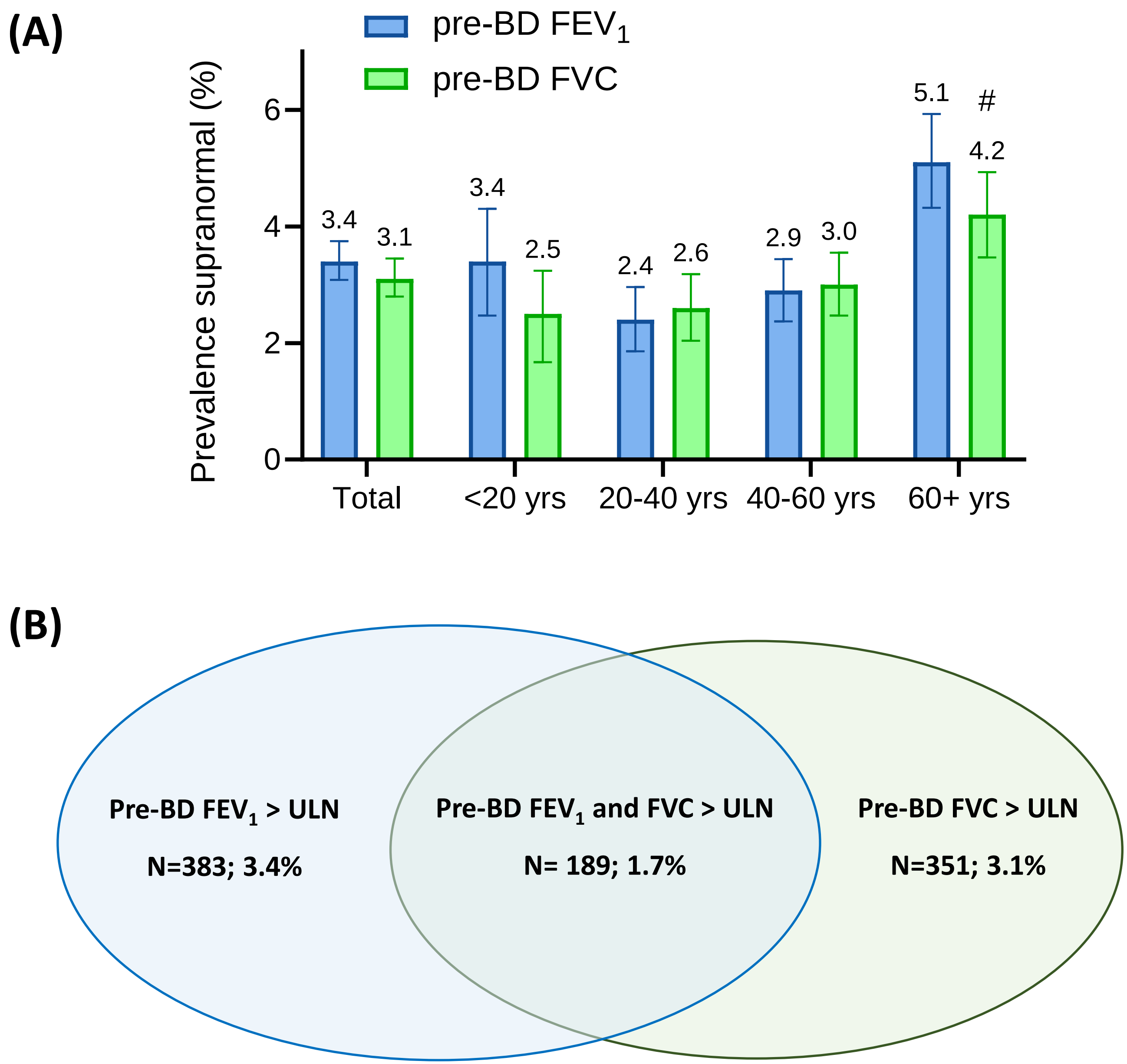
Figure 3. Forest-plots (OR and 95%CI) of factors significantly (p<0.05) and independently related to pre-BD FEV_1 >ULN (*Panel A*) and pre-BD FVC > ULN (*Panel B*) in the entire study population. Arrows indicate increased levels of the variable. BMI: body mass index; FFMI: fat free mass index; urban: urban living; hsCRP high sensitivity C-reactive protein. For further explanations, see text.

Figure 4. Correlation network of all factors identified by the multivariate logistic regression analysis in relation to supranormal (A) FEV_1 or (B) FVC values (Figure 3). The width of the links between nodes (variables) is proportional to their respective Spearman's Rho value. Continuous and dashed lines indicate a direct or inverse relationship, respectively. BMI: body mass index; FFMI: fat free mass index; urban: urban living; hsCRP high sensitivity C-reactive protein. For further explanations, see text.



LEAD Study cohort
n = 11423
Invalid spirometry
n = 196
Valid spirometry
n = 11227
FEV1 preBD < LLN or
FVC preBD < LLN
n = 1205
Analysis population
n = 10222

Figure 1



Prevalence supranormal values

Figure 2

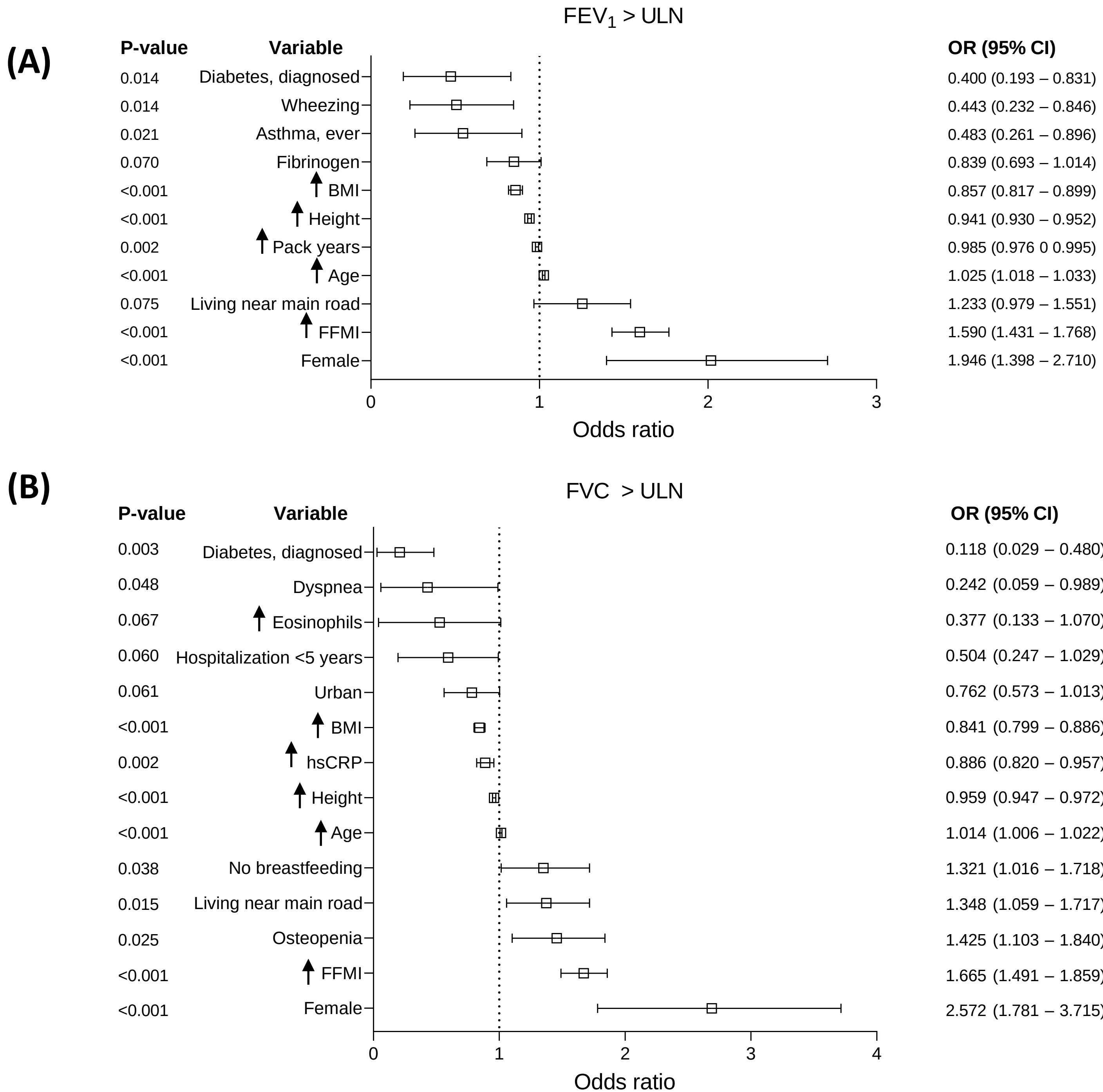
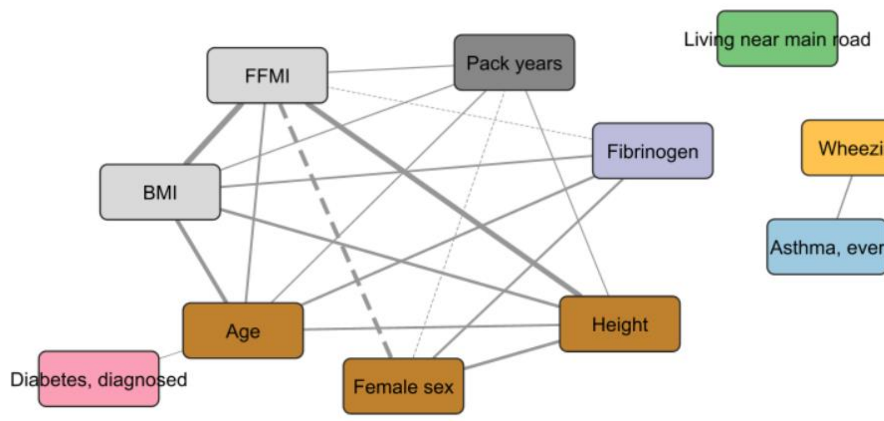

(A)
FEV1 > ULN
P-value
Variable
OR (95% CI)
0.014 Diabetes, diagnosed 0.400 (0.193 – 0.831)
0.014 Wheezing 0.443 (0.232 – 0.846)
0.021 Asthma, ever 0.483 (0.261 – 0.896)
0.070 Fibrinogen 0.839 (0.693 – 1.014)
<0.001 BMI 0.857 (0.817 – 0.899)
<0.001 Height 0.941 (0.930 – 0.952)
0.002 Pack years 0.985 (0.976 0 0.995)
<0.001 Age 1.025 (1.018 – 1.033)
0.075 Living near main road 1.233 (0.979 – 1.551)
<0.001 FFMI 1.590 (1.431 – 1.768)
<0.001 Female 1.946 (1.398 – 2.710)
0
1
2
3
Odds ratio
(B)
FVC > ULN
P-value
Variable
OR (95% CI)
0.003 Diabetes, diagnosed 0.118 (0.029 – 0.480)
0.048 Dyspnea 0.242 (0.059 – 0.989)
0.067 Eosinophils 0.377 (0.133 – 1.070)
0.060 Hospitalization <5 years 0.504 (0.247 – 1.029)
0.061 Urban 0.762 (0.573 – 1.013)
<0.001 BMI 0.841 (0.799 – 0.886)
0.002 hsCRP 0.886 (0.820 – 0.957)
<0.001 Height 0.959 (0.947 – 0.972)
<0.001 Age 1.014 (1.006 – 1.022)
0.038 No breastfeeding 1.321 (1.016 – 1.718)
0.015 Living near main road 1.348 (1.059 – 1.717)
0.025 Osteopenia 1.425 (1.103 – 1.840)
<0.001 FFMI 1.665 (1.491 – 1.859)
<0.001 Female 2.572 (1.781 – 3.715)
0
1
2
3
4
Odds ratio

Figure 3

(A) FEV_1>ULN



(B) FVC>ULN

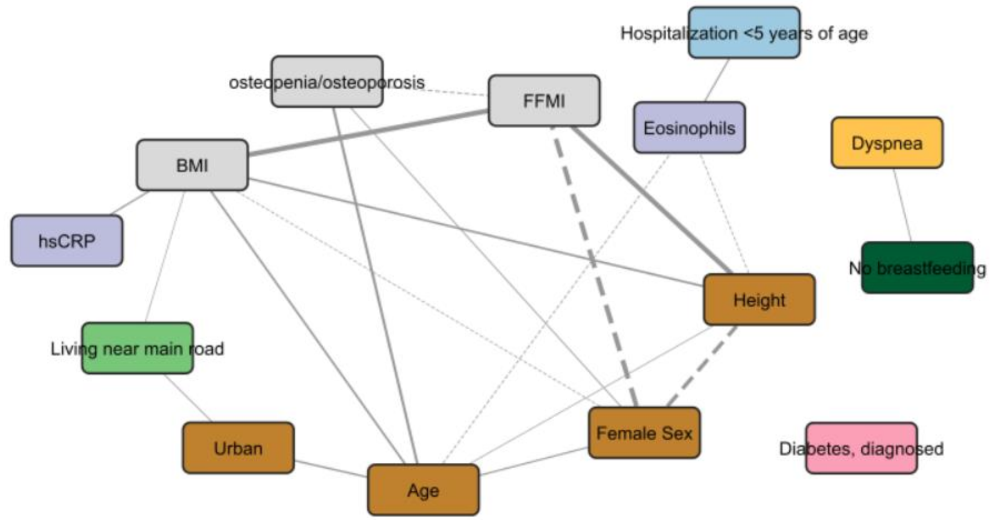


Figure 4