



Contents lists available at ScienceDirect

## Respiratory Medicine

journal homepage: [www.elsevier.com/locate/rmed](http://www.elsevier.com/locate/rmed)

## Restrictive spirometric pattern in the general adult population: Methods of defining the condition and consequences on prevalence



Helena Backman <sup>a, \*</sup>, Berne Eriksson <sup>b, c</sup>, Linnea Hedman <sup>a, d</sup>, Caroline Stridsman <sup>d</sup>,  
Sven-Arne Jansson <sup>a</sup>, Anssi Sovijärvi <sup>e</sup>, Anne Lindberg <sup>f</sup>, Eva Rönmark <sup>a</sup>, Bo Lundbäck <sup>a, c</sup>

<sup>a</sup> Department of Public Health and Clinical Medicine, Division of Occupational and Environmental Medicine/the OLIN unit, Umeå University, Umeå, Sweden

<sup>b</sup> Department of Internal Medicine, Central County Hospital of Halmstad, Halmstad, Sweden

<sup>c</sup> Krefting Research Centre, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

<sup>d</sup> Department of Health Sciences, Division of Nursing, Luleå University of Technology, Luleå, Sweden

<sup>e</sup> Dept of Clinical Physiology and Nuclear Medicine, HUS Medical Imaging Centre, Helsinki University Central Hospital, Helsinki, Finland

<sup>f</sup> Department of Public Health and Clinical Medicine, Division of Medicine/the OLIN unit, Umeå University, Umeå, Sweden

## ARTICLE INFO

## Article history:

Received 1 September 2016

Received in revised form

5 October 2016

Accepted 10 October 2016

Available online 12 October 2016

## Keywords:

Restriction

Spirometry

Prevalence

Risk factor

General population

## ABSTRACT

**Background:** Attempts have been made to use dynamic spirometry to define restrictive lung function, but the definition of a restrictive spirometric pattern (RSP) varies between studies such as BOLD and NHANES. The aim of this study was to estimate the prevalence and risk factors of RSP among adults in northern Sweden based on different definitions.

**Methods:** In 2008–2009 a general population sample aged 21–86y within the obstructive lung disease in northern Sweden (OLIN) studies was examined by structured interview and spirometry, and 726 subjects participated (71% of invited). The prevalence of RSP was calculated according to three different definitions based on pre- as well as post-bronchodilator spirometry:

1)  $FVC < 80\% \ \& \ FEV_1/FVC > 0.7$

2)  $FVC < 80\% \ \& \ FEV_1/FVC > LLN$

3)  $FVC < LLN \ \& \ FEV_1/FVC > LLN$

**Results:** The three definitions yielded RSP prevalence estimates of 10.5%, 11.2% and 9.4% respectively, when based on pre-bronchodilator values. The prevalence was lower when based on post-bronchodilator values, i.e. 7.3%, 7.9% and 6.6%. According to definition 1 and 2, the RSP prevalence increased by age, but not according to definition 3. The overlap between the definitions was substantial. When corrected for confounding factors, manual work in industry and diabetes with obesity were independently associated with an increased risk for RSP regardless of definition.

**Conclusions:** The prevalence of RSP was 7–11%. The prevalence estimates differed more depending on the choice of pre- compared to post-bronchodilator values than on the choice of RSP definition. RSP was, regardless of definition, independently associated with manual work in industry and diabetes with obesity.

© 2016 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

**Abbreviations:** ATS, American Thoracic Society; BMI, Body Mass Index; BOLD, Burden of Obstructive Lung Disease; CI, Confidence Interval; ERS, European Respiratory Society; FEV<sub>1</sub>, Forced expiratory volume in one second; FVC, Forced expiratory volume; GA2LEN, Global Allergy and Asthma European Network; GLI, Global Lung Initiative; IHD, Ischemic Heart Disease; LLN, Lower Limit of Normal; NHANES, National Health and Nutrition Examination Survey; OLIN, Obstructive Lung Disease in Northern Sweden; OR, Odds Ratio; Post-BD, After bronchodilation; Pre-BD, Before bronchodilation; RSP, Restrictive Spirometric Pattern; TLC, Total Lung Capacity.

\* Corresponding author. Department of Public Health and Clinical Medicine, Division of Occupational and Environmental Medicine/the OLIN Unit, Umeå University, 90 187 Umeå, Sweden.

E-mail address: [helena.backman@nll.se](mailto:helena.backman@nll.se) (H. Backman).

### 1. Introduction

Restrictive lung function is defined as reduced lung expansion expressed as a decreased total lung capacity (TLC). It may reflect several underlying conditions and diseases, such as interstitial lung diseases, pleural effusions and disorders, thoracic deformities, neuromuscular diseases, diaphragmatic disorders, obesity, heart failure, pregnancy and pain [1]. Interstitial lung diseases comprise more than 200 diagnoses including idiopathic pulmonary fibrosis, several pneumoconiosis, sarcoidosis and several other conditions

[2,3]. The prevalence of most of these conditions is low, for instance the prevalence of idiopathic pulmonary fibrosis has been estimated at about 0.1% or even less [4].

Attempts have been made to use dynamic spirometry to identify restrictive lung function, using a low FVC and a normal FEV<sub>1</sub>/FVC ratio as a definition of a restrictive lung function [5]. Dynamic spirometry has limitations in identifying restrictive lung diseases [6,7], but it can effectively exclude a restrictive disease when FVC is normal and its specificity increases when the FEV<sub>1</sub>/FVC ratio is taken into account [7,8]. Further, a recent review stresses the many clinical, public health and eventually therapeutic implications of identifying subjects with a restrictive spirometry pattern (RSP) [9], since RSP is associated with high symptom burden, comorbidities and adverse outcomes including mortality.

The estimates of prevalence of restrictive conditions based on dynamic spirometry vary considerably, probably due to the various definitions used as described in the recent review [9]. Most commonly, fixed thresholds such as FVC < 80% of predicted and a FEV<sub>1</sub>/FVC ratio >0.7 have been utilized for the definition of RSP, but other types of thresholds are gaining ground. Further, most studies have used pre-bronchodilator (pre-BD) spirometry data for defining RSP, while in the Burden of Obstructive Lung Disease (BOLD) study post-bronchodilator (post-BD) data were used [8]. Data from the US National Health and Nutrition Examination surveys (NHANES) have presented consistent results with prevalence of RSP on general population level varying from 5.4% to 9.2% [10–14]. Prevalence estimates from other studies vary from 3% to 13% [15–19], while the prevalence among the BOLD centers vary from 4% to upward of 50% [8]. Co-existing diseases such as diabetes, obesity, cardiovascular and rheumatic diseases and other risk factors for RSP have been studied mainly in the US. To date, there are no studies comparing different definitions of RSP based on both pre- and post-BD spirometry in the general population.

The aim of this study was to estimate the prevalence of RSP in an adult general population using different definitions of restrictive spirometry, and to study associated risk factors and co-existing diseases.

## 2. Materials and methods

### 2.1. Study population

In 2006 a random sample in ages 20–69 years in Norrbotten county in Northern Sweden,  $n = 7997$ , was invited to participate in a postal questionnaire survey [20]. Another randomly selected population sample in ages 30–84 years, which had participated in a similar questionnaire survey in 1996 [21], was also invited,  $n = 7004$ . Overall 12,055 subjects (80% of the invited) participated [22].

Of the questionnaire responders, a randomly selected sample,  $n = 1016$ , after stratification for the sex and age distribution of the county population, was invited to clinical examinations including pre- and post-bronchodilator (BD) spirometry and a structured interview in 2008–2009. Of the invited, 726 (71.5%) subjects performed spirometry with adequate technique and completed the interview [22], with mean age 53 years (range 21–86 years) and 50% women. The participants at the clinical examinations were representative for the entire cohort with respect to age, gender and prevalence of respiratory symptoms and diseases and their comorbidities [23]. The Study was approved by the Regional Ethical Review Board at Umeå University.

### 2.2. Questionnaire

The questionnaire consists of a self-administrated short version

for postal surveys [24] and a version for interviews [25]. It has been used in several epidemiological studies [26–29] and is validated against the GA2LEN questionnaire [30]. The questions are focused on respiratory symptoms and diseases, their comorbidities, allergy, medication, family history of asthma and allergic diseases, smoking habits, occupation, area of domicile and other potential risk factors for respiratory diseases.

### 2.3. Spirometry

A Masterscope (Jaeger, Germany) flow-volume spirometer was used. The procedure followed the ATS/ERS recommendations [31] but with a reproducibility criterion of  $\leq 5\%$  deviation from the second highest value [32]. At least three and maximum six forced vital capacity (FVC) maneuvers were performed. A reversibility test was performed using 0.4 mg salbutamol powder via discus. Reference values for spirometry derived from the population living in the study area were used [33]. The Global Lung Initiative (GLI) reference values [34] were used in sensitivity analyses presented in the Results section and Table A.1.

### 2.4. Definitions

RSP was defined as a decreased FVC in combination with a normal or increased FEV<sub>1</sub>/FVC ratio. The definitions thereof are based both on fixed thresholds, i.e. FVC < 80% of predicted and ratio of FEV<sub>1</sub>/FVC > 0.7, and also on the lower limit of normal (LLN), i.e. the fifth percentile (approximately corresponding to a Z-score < -1.645). Both pre- and post-BD spirometry was used, where post-BD values were defined as the highest of pre- and post-BD results. The use of LLN is strongly recommended by the ERS/ATS task force on standardization of lung function testing [31]. Three different definitions based on pre- and post-BD values respectively were analyzed (Table 1). Severity grading was based both on the level of FEV<sub>1</sub> as recommended by the ERS/ATS task force [31] and on the level of FVC, and the limit for severity was defined as <70% of predicted for both. Subjects with obstructive spirometry were excluded from analyses comparing RSP with normal spirometry.

Information about heart diseases, hypertension, diabetes and rheumatic disease was collected through interviews. Ischemic heart disease (IHD) was defined as a history of myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention or angina pectoris. Any heart disease was defined as a report of IHD, heart failure, arrhythmia or other heart disease. Height and weight was measured and Body Mass Index (BMI, kg/m<sup>2</sup>) calculated. Underweight was classified as BMI < 20, normal weight as  $20 \leq \text{BMI} < 25$ , overweight as  $25 \leq \text{BMI} < 30$  and obesity as BMI  $\geq 30$ . The classification of socio-economic status was based on occupation. Smoking habits were classified as ever-smokers (current or ex-smokers) and never-smokers, and by number of pack-years. Ex-smokers were defined as those who had smoked for at least one year but not during the last 12 months.

### 2.5. Analyses

The Fisher's exact test (two-sided) was used for bivariate comparisons of proportions. For comparisons of proportions across more than two groups, Mantel-Haenszel test for trend was used. A  $p$ -value <0.05 was considered statistically significant. Multiple logistic regression was used to test independent risk factors for RSP with results presented as adjusted odds ratios (OR) with 95% confidence intervals (CI). Variables significantly associated with RSP in unadjusted analyses (Table A.2) were included in the regression analyses. An interaction term between diabetes and obesity was also analyzed. Age was dichotomized in the regression analyses

**Table 1**  
Definitions of restrictive spirometric pattern (RSP).

	Definition 1 <sup>a</sup>	Definition 2 <sup>a</sup>	Definition 3 <sup>a</sup>
Normal spirometry	FVC > 80% pred & FEV1/FVC > 0.7	FVC > 80% pred & FEV1/FVC > LLN	FVC > LLN & FEV1/FVC > LLN
Restrictive spirometric pattern	FVC < 80% pred & FEV1/FVC > 0.7	FVC < 80% pred & FEV1/FVC > LLN	FVC < LLN & FEV1/FVC > LLN
Obstructive spirometry	FEV1/FVC < 0.7	FEV1/FVC < LLN	FEV1/FVC < LLN

pred = predicted.

LLN = Lower limit of Normal defined as the fifth percentile [31].

<sup>a</sup> Definitions 1–3 are analyzed based on both pre-bronchodilator and post-bronchodilator values, respectively.

with 60 years as cut-off as prevalence of restrictive spirometry increases from middle ages.

### 3. Results

#### 3.1. Participation and basic characteristics

Of the invited 504 women and 512 men, 73% and 70%, participated. Current smoking was more common among women, 17.7%, than among men, 11.8% ( $p = 0.028$ ). In contrast, men tended to have more pack-years than women. Among women, 24.2% were obese versus 19.0% among men ( $p = 0.104$ ), while the inverse was true for overweight. The prevalence of both pre- and post-BD FVC < 80% increased considerably by age, but less so for FVC < LLN (Table 2).

#### 3.2. Prevalence and severity of restrictive spirometric pattern

The prevalence of pre-BD RSP was highest based on the FVC < 80% & FEV1/FVC > LLN definition, 11.2%, while it was 10.5% for FVC < 80% & FEV1/FVC > 0.7, and 9.4% for FVC < LLN & FEV1/FVC > LLN. The prevalence based on post-BD spirometry followed the same pattern but was lower, ranging from 7.9 to 6.6% (Table 3). The prevalence of RSP increased by age and was most common in age > 60 years according to all definitions, except for the post-BD FVC < LLN & FEV1/FVC > LLN definition. Further, pre-BD RSP tended to be somewhat more common among men (Table 3). There was a considerable overlap between all three pre-BD definitions as well as between all three post-BD definitions of RSP (Table 4). The proportion among subjects with post-BD RSP with higher pre- than post-BD values of FVC and FEV1/FVC was approximately 1/3 and of FEV1 approximately 1/5 (Table A.3). Approximately 25% of the subjects with pre-BD RSP had FVC < 70% of predicted (Fig. 1), while

approximately 10–12% had FEV1 < 70% of predicted.

#### 3.3. Symptoms associated with restrictive spirometric pattern

Most respiratory symptoms were more common among subjects with RSP than among subjects with normal spirometry. In general, the prevalence of symptoms was of similar magnitude for the pre- and post-BD definitions of RSP. The most common symptoms among the subjects with RSP were any wheeze last 12 months, 41.7%–46.1%, and sputum production, 37.5%–44.7% (Table A.4). The greatest relative differences in symptom prevalence were found for dyspnea, mMRC grades  $\geq 2$  and  $\geq 3$ , which were 2.1–7.8 times more common among subjects with RSP than among subjects with normal spirometry.

#### 3.4. Risk factors

In unadjusted analyses, *diabetes* (OR 4.3–5.3), *any heart disease* (OR 2.0–2.7) and *obesity* (OR 2.0–2.6) were significantly associated with RSP by all pre-BD definitions. Neither *male sex* nor *ever smoking* was significantly associated with RSP (Table A.2).

In adjusted analyses, the socio-economic group *manual work in industry* was significantly and independently associated with RSP regardless of definition with ORs ranging from 1.76 to 3.10 (Tables 5 and 6). *Diabetes* yielded high and significant odds ratios in the three pre-BD analyses, varying from 2.39 to 3.16. *Age > 60 years* was significantly associated with the pre-BD FVC < 80% & FEV1/FVC > 0.7 and FVC < 80% & FEV1/FVC > LLN definitions of RSP, while it was not with the FVC < LLN & FEV1/FVC > LLN definition. *Current smoking*, *hypertension* and *obesity* were significantly associated with some definitions. Neither *rheumatic disease* nor *any heart disease* was independently associated with any of the RSP definitions.

**Table 2**  
Participant characteristics by age group and sex.

Participant characteristics	Sex			Age group				All N = 726
	Women	Men	P-value	22–40y	41–60y	61–84y	P-value	
	N = 368	N = 358		N = 167	N = 312	N = 247		
Never-smokers	49.9%	53.5%		70.7%	45.7%	46.3%		51.7%
Ex-smokers	32.4%	34.7%		15.6%	37.9%	40.2%		33.6%
Smokers	17.7%	11.8%	0.076	13.8%	16.4%	13.4%	0.003	13.4%
Never-smokers	49.9%	53.5%		70.7%	45.7%	46.3%		51.7%
Pack-years < 10	26.4%	21.0%		25.7%	25.1%	20.7%		23.8%
10 $\geq$ Pack-years < 20	13.4%	8.1%		3.0%	16.1%	9.3%		10.8%
Pack-years $\geq$ 20	10.4%	17.4%	0.519	0.6%	13.2%	23.6%	<0.001	13.8%
Normal or underweight	37.0%	26.3%		35.9%	34.6%	25.1%		31.7%
Overweight	38.9%	54.7%		44.3%	44.2%	51.4%		46.7%
Obesity	24.2%	19.0%	0.057	19.8%	21.2%	23.5%	0.018	21.6%
Pre-bronchodilator FVC < 80%	10.9%	13.4%	0.308	7.2%	8.3%	20.2%	<0.001	12.1%
Post-bronchodilator FVC < 80%	8.4%	8.7%	1.000	6.0%	5.8%	13.8%	0.002	8.5%
Pre-bronchodilator FVC < LLN	9.5%	11.5%	0.399	7.8%	9.0%	14.2%	0.027	10.5%
Post-bronchodilator FVC < LLN	7.1%	7.5%	0.887	7.8%	5.8%	8.9%	0.547	7.3%

P-value = Fisher's exact test or Mantel Haenzel test for trend, as appropriate.

Pack-years represent smoking history among ever-smokers.

Two subjects lack information regarding smoking history.

**Table 3**

Prevalence of restrictive spirometric pattern (RSP) by age group and sex, according to three different definitions based on pre- and post-bronchodilator spirometry.

Definition of RSP		Sex			Age group				All
		Women	Men	P-value	22–39y	40–60y	61–84y	P-value	
FVC < 80% & FEV <sub>1</sub> /FVC > 0.7	pre	9.0%	12.0%	0.185	7.2%	8.0%	15.8%	0.003	10.5%
	post	7.1%	7.5%	0.887	6.0%	5.4%	10.5%	0.053	7.3%
FVC < 80% & FEV <sub>1</sub> /FVC > LLN	pre	10.3%	12.0%	0.482	7.2%	8.0%	17.8%	<0.001	11.2%
	post	8.2%	7.5%	0.784	6.0%	5.4%	12.1%	0.011	7.9%
FVC < LLN & FEV <sub>1</sub> /FVC > LLN	pre	8.7%	10.1%	0.611	7.8%	8.3%	11.7%	0.147	9.4%
	post	6.8%	6.4%	0.882	7.8%	5.4%	7.3%	0.954	6.6%

P-value = Fisher's exact test or Mantel Haenzel test for trend, as appropriate.

pre = based on pre-bronchodilator spirometry.

post = based on post-bronchodilator spirometry.

**Table 4**

Overlap (n) between different definitions of restrictive spirometric pattern (RSP).

Definition of RSP	Prevalence	Overlap (n)					
		pre			post		
		FVC < 80% & FEV <sub>1</sub> /FVC > 0.7	FVC < 80% & FEV <sub>1</sub> /FVC > LLN	FVC < LLN & FEV <sub>1</sub> /FVC > LLN	FVC < 80% & FEV <sub>1</sub> /FVC > 0.7	FVC < 80% & FEV <sub>1</sub> /FVC > LLN	FVC < LLN & FEV <sub>1</sub> /FVC > LLN
	n (%)	76 (10.5%)	81 (11.2%)	68 (9.4%)	53 (7.3%)	57 (7.9%)	48 (6.6%)
pre	FVC < 80% & FEV <sub>1</sub> /FVC > 0.7	76 (10.5%)	76	*	*	*	*
	FVC < 80% & FEV <sub>1</sub> /FVC > LLN	81 (11.2%)	76	81	*	*	*
	FVC < LLN & FEV <sub>1</sub> /FVC > LLN	68 (9.4%)	60	64	68	*	*
post	FVC < 80% & FEV <sub>1</sub> /FVC > 0.7	53 (7.3%)	52	53	46	53	*
	FVC < 80% & FEV <sub>1</sub> /FVC > LLN	57 (7.9%)	53	57	50	53	57
	FVC < LLN & FEV <sub>1</sub> /FVC > LLN	48 (6.6%)	44	47	48	39	42

pre = based on pre-bronchodilator spirometry.

post = based on post-bronchodilator spirometry.

RSP = Restrictive spirometric pattern.

Interaction analysis revealed that although neither *diabetes without obesity* nor *obesity without diabetes* was significantly associated with any RSP definition, *diabetes with obesity* yielded high and significant adjusted ORs for all six definitions of RSP, ranging from 5.38 to 7.81 (Fig. 2).

### 3.5. Sensitivity analyses

When the GLI reference values were applied, the estimates of RSP prevalence were low. The pre- and post-BD prevalence estimates varied from 2.8% to 4.7% and from 2.1% to 2.9%, respectively (Table A.1). In adjusted risk analyses, *manual work in industry* was significantly associated with RSP irrespectively how RSP was defined (OR 2.89–5.13), and so was *hypertension* (OR 2.83–3.69). Similar to when the OLIN reference values were used, neither *obesity without diabetes* nor *diabetes without obesity* was associated with RSP, while *diabetes with obesity* yielded ORs from 1.87 to 18.79.

## 4. Discussion

The prevalence of restrictive spirometric pattern (RSP) was 9–11% when based on pre-BD values, which is the most commonly used definition of RSP [7,9–18]. Use of post-BD values yielded a prevalence of 7–8%. The overlap between the different definitions was substantial.

The prevalence increased by age in line with previous results from the NHANES [10,11], however, not significantly using the FVC < LLN & FEV<sub>1</sub>/FVC > LLN definition of RSP. No significant gender differences were found.

The prevalence of the pre-BD FVC < 80% & FEV<sub>1</sub>/FVC > 0.7 definition, 10.7%, is similar to the 8–12% reported from the NHANES I [10], two other studies from the USA [15,17], and one from Italy [16], but somewhat higher than the 6.5–7.6% found in the NHANES III

1988–1994 and the NHANES 2007–2010 [13].

The data from the NHANES III 1988–1994 and NHANES 2007–2010 have also been analyzed using the FVC < LLN & FEV<sub>1</sub>/FVC > LLN definition [14] which yielded a prevalence of 7.2% in the NHANES III and 5.4% in the latter survey. These results are similar to the 7.6% and 6.5%, respectively, which the NHANES found based on the most commonly used definition, i.e. FVC < 80% & FEV<sub>1</sub>/FVC > 0.7 [13]. These studies suggest some decrease in prevalence of RSP in USA over the 15–20 year period.

Most studies define RSP as a decreased pre-BD FVC and a normal or elevated FEV<sub>1</sub>/FVC ratio. A Spanish multi-center study using this definition based on the ECSC reference values yielded prevalence estimates ranging from 5% to 19% between sites [19]. The BOLD study [8] used a definition of FEV<sub>1</sub> < 80% and FEV<sub>1</sub>/FVC > 0.7 based on post-BD spirometry. The NHANES reference values were used for all centers in the BOLD study and yielded a large variance in prevalence; from 4–8% in Australia and 5–6% in Vancouver to upwards 50% in the Philippines and India [8]. ATS/ERS presents a severity classification for restrictive subjects based on FEV<sub>1</sub>% of predicted [31], and 10–12% of those with RSP had FEV<sub>1</sub><70% of predicted in our study. We argue, however, that severity of restrictive lung disease could be based on FVC because it limits possible misclassification of volume-responders as being restrictive and the fact that restriction itself is defined as a reduction of the lung volume.

In unadjusted analyses the co-morbid conditions diabetes and heart disease were most consistently associated with RSP. In adjusted analyses, only the association between pre-BD RSP and diabetes remained. An association between RSP and heart diseases has been found in several NHANES surveys [10–14], the BOLD study [8] and some other studies [15,17,18]. In line with our results, an association with diabetes was found in both the BOLD [8] and NHANES [11,12,14] studies. The NHANES and BOLD studies have

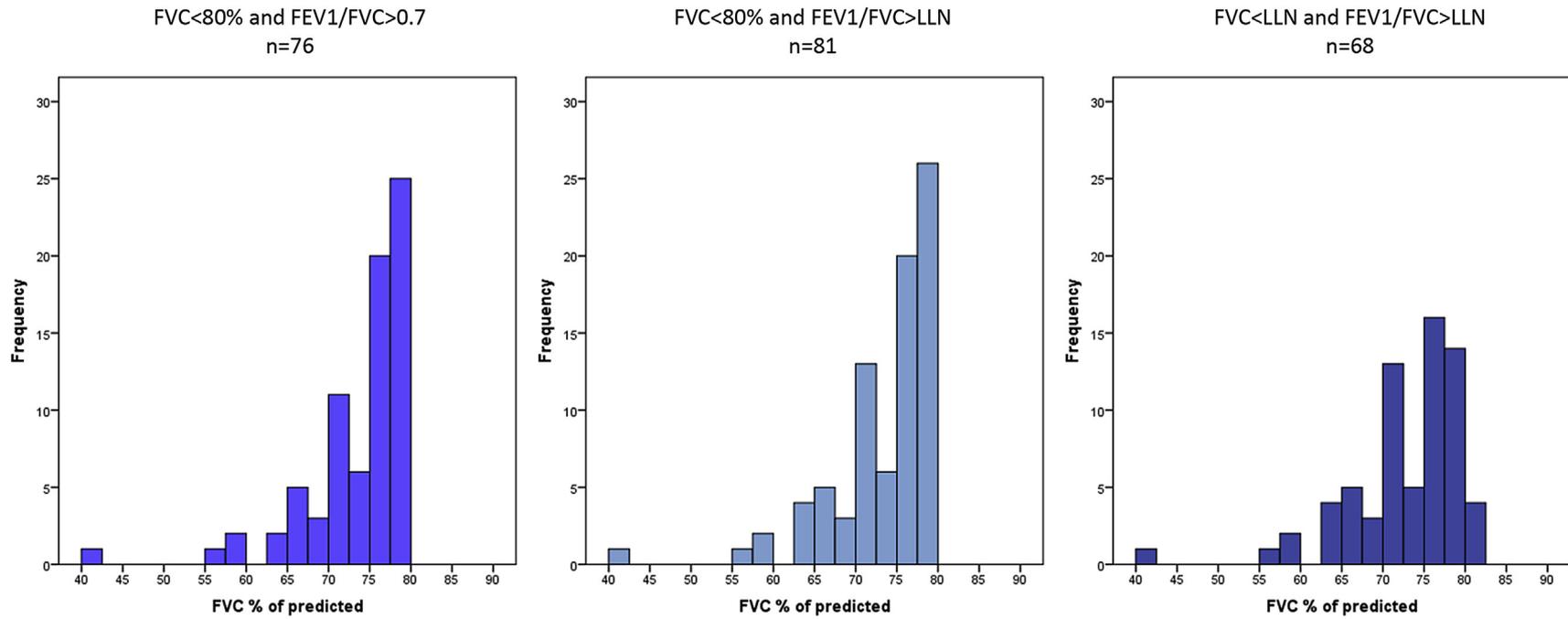


Fig. 1. Histograms of pre-bronchodilator FVC % of predicted among subjects with restrictive spirometric pattern according to the three different definitions.

**Table 5**  
Risk factors for pre-bronchodilator restrictive spirometric pattern (RSP) according to different definitions (adjusted analyses).

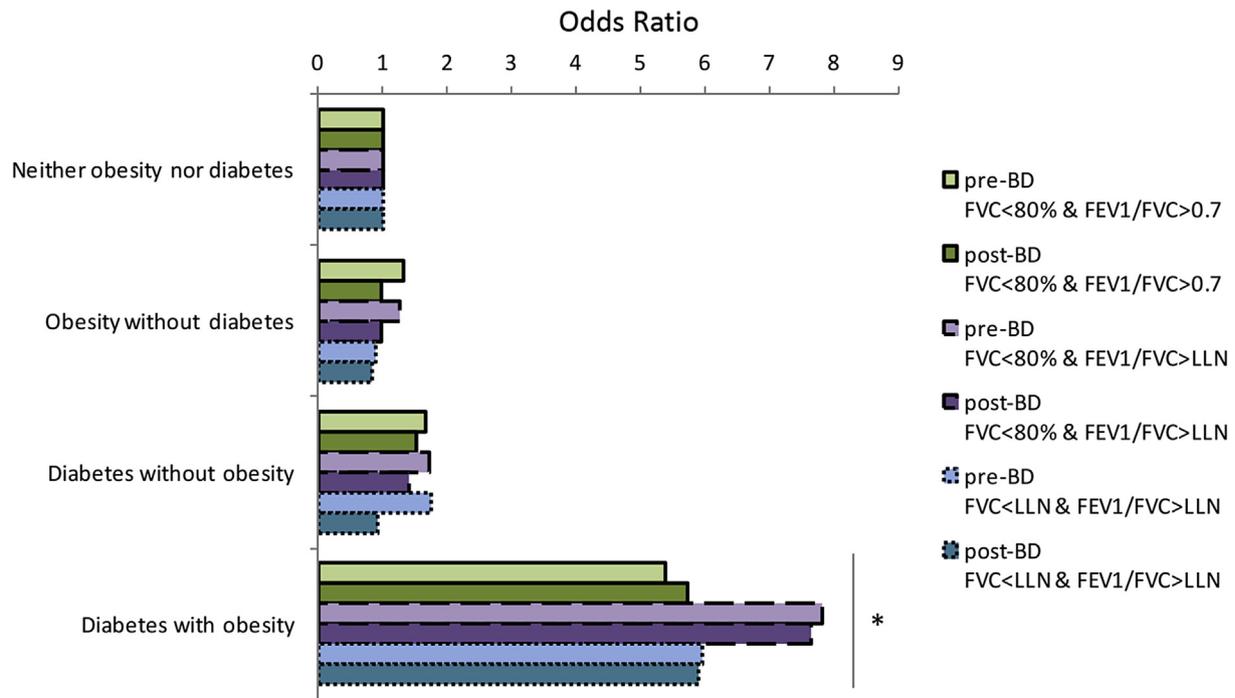
	FVC < 80% & FEV <sub>1</sub> /FVC > 0.7		FVC < 80% & FEV <sub>1</sub> /FVC > LLN		FVC < LLN & FEV <sub>1</sub> /FVC > LLN	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Age > 60 years	<b>1.97</b>	<b>(1.14–3.42)</b>	<b>1.89</b>	<b>(1.11–3.23)</b>	0.95	(0.52–1.72)
Current smoking	1.71	(0.85–3.44)	1.73	(0.88–3.41)	<b>2.27</b>	<b>(1.14–4.52)</b>
Manual work in industry	<b>1.89</b>	<b>(1.07–3.34)</b>	<b>1.76</b>	<b>(1.00–3.09)</b>	<b>2.16</b>	<b>(1.21–3.88)</b>
Any heart disease	1.60	(0.84–3.04)	1.47	(0.79–2.74)	1.44	(0.72–2.87)
Rheumatic disease	2.11	(0.81–5.52)	1.65	(0.65–4.21)	1.69	(0.62–4.59)
Hypertension	1.55	(0.89–2.72)	1.61	(0.93–2.76)	<b>2.16</b>	<b>(1.20–3.90)</b>
Obesity	1.52	(0.87–2.65)	1.55	(0.90–2.66)	1.14	(0.63–2.08)
Diabetes	<b>2.39</b>	<b>(1.08–5.27)</b>	<b>3.02</b>	<b>(1.44–6.36)</b>	<b>3.16</b>	<b>(1.42–7.02)</b>

OR = Odds Ratio from multiple logistic regression models, CI = Confidence Interval.  
Subjects with normal spirometry as reference.  
Significant associations are bolded.

**Table 6**  
Risk factors for post-bronchodilator restrictive spirometric pattern (RSP) according to different definitions (adjusted analyses).

	FVC < 80% & FEV <sub>1</sub> /FVC > 0.7		FVC < 80% & FEV <sub>1</sub> /FVC > LLN		FVC < LLN & FEV <sub>1</sub> /FVC > LLN	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Age > 60y	1.79	(0.94–3.42)	1.83	(0.98–3.41)	0.88	(0.44–1.76)
Current smoking	<b>2.51</b>	<b>(1.34–4.72)</b>	<b>2.44</b>	<b>(1.32–4.51)</b>	1.87	(0.96–3.64)
Manual work in industry	<b>2.77</b>	<b>(1.16–6.58)</b>	<b>3.10</b>	<b>(1.37–7.05)</b>	<b>2.62</b>	<b>(1.04–6.60)</b>
Any heart disease	1.18	(0.55–2.57)	1.19	(0.57–2.51)	0.92	(0.39–2.20)
Rheumatic disease	0.96	(0.26–3.55)	0.86	(0.23–3.18)	1.18	(0.33–4.25)
Hypertension	1.25	(0.65–2.41)	1.38	(0.73–2.58)	1.21	(0.61–2.40)
Obesity	1.90	(0.87–4.14)	<b>2.08</b>	<b>(1.00–4.30)</b>	1.65	(0.75–3.65)
Diabetes	1.61	(0.83–3.11)	1.54	(0.81–2.93)	1.91	(0.96–3.80)

OR = Odds Ratio from multiple logistic regression models, CI = Confidence Interval.  
Subjects with normal spirometry as reference.  
Significant associations are bolded.



**Fig. 2.** The risk for restrictive spirometric pattern among subjects with obesity without diabetes, diabetes without obesity, and diabetes with obesity. Odds Ratios with neither obesity nor diabetes as reference, adjusted for age, any heart disease, rheumatic disease, hypertension, manual work in industry, and smoking. BD = bronchodilator. \*Diabetes with obesity was a significant risk factor ( $p < 0.05$ ) regardless of definition of RSP.

found RSP to be associated with both obesity and underweight [8,11]. Although we found an interaction between obesity and diabetes, our study did not find obesity alone to be independently

associated with RSP.

Only a few studies have focused on risk factors for RSP on population level. Among other risk factors, manual work in

industry was significantly and independently associated with RSP regardless of definition and choice of reference values. The found association is of great interest, as early interstitial or pleural involvement without a clinical disease might be caused by occupational exposures [35]. However, among Swedish construction workers, the prevalence of restrictive lung function was only 4% [36]. As found by others [11,16], age was significantly associated with RSP when the condition was based on the  $FVC < 80\% \& FEV_1/FVC > 0.7$  definition, but not when the  $FVC < LLN \& FEV_1/FVC > LLN$  definition was applied.

The impact of reference values for interpretation of spirometry findings is exemplified by use of the GLI reference values [34], which in our study population resulted in considerably lower prevalence of RSP. The reason for the large difference in prevalence is that the GLI reference values for FVC results in lower FVC predictions than the reference values for the population under study [37]. The choice of reference values may at least in part explain the low prevalence of RSP, i.e. 3–4%, found in previous Swedish studies [18,36]. Also the recent review on RSP notes that discrepancies in RSP prevalence may be attributable to use of different reference values [9].

Assessment of total lung capacity (TLC) is the best test to correctly differentiate restrictive lung function from normal and obstructive lung function. However, there is a lack in the literature of more recent studies focusing on TLC in the general population. The normal range has been estimated as quite wide, as exemplified by an elderly consensus report [38] and by a study in Brazil [39]. A few population studies have measured TLC, but have not focused their publications directly on TLC [40]. Instead of focusing on TLC, several studies have defined restrictive lung function by use of dynamic spirometry alone [8,10–13,15–18]. We have found only one study that has validated this issue. The study found that about 60% of those with a RSP defined as pre-BD  $FVC < 80\% \& FEV_1/FVC > 0.7$  to have a true restrictive lung function defined as a low total lung capacity (TLC) [7]. Thus, the use of dynamic spirometry leads to an overestimation of the prevalence of restrictive lung function where air trapping in small airways contributes. On the other hand, only 3% of those with  $FVC > 80\%$  of predicted values had a restrictive lung function defined as a low TLC. Consequently, dynamic spirometry can effectively exclude subjects who are unlikely to have restrictive lung function from undergoing costly examinations of TLC [7].

This study is the first to compare different definitions of RSP based on both pre- and post-BD values. The high participation rate contributes to the validity of the results. Repeated control of methods has been performed with regular time intervals. Only limited bias caused by non-response and non-participation has been found [41]. The questionnaire has recently been validated [30], and the staff of nurses and technicians is well trained. As mentioned, dynamic spirometry has limitations in identifying restrictive lung function. In case dynamic spirometry is used for defining RSP, we believe LLN results should be preferred as the use of fixed ratio overestimates the impact of age on the results. Also, our results put emphasis on the use of post-bronchodilator spirometry when defining RSP as volume responders otherwise could incorrectly be classified as having restriction. This assumption is supported by the fact that an increase in the  $FEV_1/FVC$  ratio was observed in about 70% of the cases.

In conclusion, restrictive spirometric pattern is common with a prevalence of 9–11% based on pre-bronchodilator values and 7–8% based on post-bronchodilator values. The choice of reference values affected the prevalence. Irrespective of definition, restrictive spirometric pattern was independently associated with manual work in industry and diabetes with obesity.

## Acknowledgements

HB and BL are guarantors of the study and takes responsibility for the content of the manuscript, including the data and analysis. HB and BL planned and designed the manuscript, wrote the first drafts and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. BE, CS, LH, AS, AL and ER all contributed substantially to the study design, data analysis and interpretation as well as to the writing and finalizing of the manuscript. Further, the OLIN staff Ann-Christine Jonsson, Sigrid Sundberg and Britt-Marie Eklund are acknowledged for excellent data collection. Financial support was received mainly from The Swedish Heart & Lung Foundation (20050428, 20090244, and 20150488), The Swedish Research Council (80589701), ALF (216371)—a regional agreement between Umeå University and Norrbotten County Council, Norrbotten County Council (NLL-574941), the Swedish Asthma-Allergy Foundation and Visare Norr.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2016.10.005>.

## References

- [1] R.C. Stansbury, D.M. Mannino, Chapter on Diseases Associated with Restrictive Lung Function Impairment, ERS Monograph, European Respiratory Society, 2009, pp. 142–149. Respiratory Diseases in the Elderly.
- [2] B. Bradley, H.M. Branley, J.J. Egan, M.S. Greaves, D.M. Hansell, N.K. Harrison, et al., Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society, *Thorax* 63 (Suppl. 5) (2008 Sep) v1–58.
- [3] D. Valeyre, B. Duchemann, H. Nunes, Y. Uzunhan, I. Annesi-Maesano, Chapter on Interstitial Lung Diseases, ERS Monograph, European Respiratory Society, 2014, pp. 79–87. Respiratory Epidemiology.
- [4] D.B. Coultas, R.E. Zumwalt, W.C. Black, R.E. Sobonya, The epidemiology of interstitial lung diseases, *Am. J. Respir. Crit. Care Med.* 150 (4) (1994 Oct) 967–972.
- [5] R.O. Crapo, Pulmonary-function testing, *N. Engl. J. Med.* 331 (1) (1994 Jul 7) 25–30.
- [6] American Thoracic Society, Lung function testing: selection of reference values and interpretative strategies, *Am. Rev. Respir. Dis.* 144 (5) (1991 Nov) 1202–1218.
- [7] S.D. Aaron, R.E. Dales, P. Cardinal, How accurate is spirometry at predicting restrictive pulmonary impairment? *Chest* 115 (3) (1999 Mar) 869–873.
- [8] D.M. Mannino, M.A. McBurnie, W. Tan, A. Kocabas, J. Anto, W.M. Vollmer, et al., Restricted spirometry in the burden of lung disease study, *Int. J. Tuberc. Lung Dis.* 16 (10) (2012 Oct) 1405–1411.
- [9] M.S. Godfrey, M.D. Jankowich, The vital capacity is vital: epidemiology and clinical significance of the restrictive spirometry pattern, *Chest* 149 (1) (2016 Jan) 238–251.
- [10] D.M. Mannino, A.S. Buist, T.L. Petty, P.L. Enright, S.C. Redd, Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study, *Thorax* 58 (5) (2003 May) 388–393.
- [11] D.M. Mannino, E.S. Ford, S.C. Redd, Obstructive and restrictive lung disease and functional limitation: data from the Third National Health and Nutrition Examination, *J. Intern Med.* 254 (6) (2003 Dec) 540–547.
- [12] D.M. Mannino, F. Holguin, B.I. Pavlin, J.M. Ferdinands, Risk factors for prevalence of and mortality related to restriction on spirometry: findings from the First National Health and Nutrition Examination Survey and follow-up, *Int. J. Tuberc. Lung Dis.* 9 (6) (2005 Jun) 613–621.
- [13] E.S. Ford, D.M. Mannino, A.G. Wheaton, W.H. Giles, L. Presley-Cantrell, J.B. Croft, Trends in the prevalence of obstructive and restrictive lung function among adults in the United States: findings from the National Health and Nutrition Examination surveys from 1988–1994 to 2007–2010, *Chest* 143 (5) (2013 May) 1395–1406.
- [14] L. Kurth, E. Hnizdo, Change in prevalence of restrictive lung impairment in the U.S. population and associated risk factors: the National Health and Nutrition Examination Survey (NHANES) 1988–1994 and 2007–2010, *Multidiscip. Respir. Med.* 10 (1) (2015 Feb 28), 7-015-0003-6. eCollection 2015.
- [15] A.K. Johnston, D.M. Mannino, G.W. Hagan, K.J. Davis, V.A. Kiri, Relationship between lung function impairment and incidence or recurrence of cardiovascular events in a middle-aged cohort, *Thorax* 63 (7) (2008 Jul) 599–605.
- [16] S. Scarlata, C. Pedone, F.L. Fimognari, V. Bellia, F. Forastiere, R.A. Incalzi, Restrictive pulmonary dysfunction at spirometry and mortality in the elderly,

- Respir. Med. 102 (9) (2008 Sep) 1349–1354.
- [17] S. Guerra, D.L. Sherrill, C. Venker, C.M. Ceccato, M. Halonen, F.D. Martinez, Morbidity and mortality associated with the restrictive spirometric pattern: a longitudinal study, *Thorax* 65 (6) (2010 Jun) 499–504.
- [18] B. Eriksson, A. Lindberg, H. Mullerova, E. Ronmark, B. Lundback, Association of heart diseases with COPD and restrictive lung function—results from a population survey, *Respir. Med.* 107 (1) (2013 Jan) 98–106.
- [19] J.B. Soriano, M. Miravittles, F. Garcia-Rio, L. Munoz, G. Sanchez, V. Sobradillo, et al., Spirometrically-defined restrictive ventilatory defect: population variability and individual determinants, *Prim. Care Respir. J.* 21 (2) (2012 Jun) 187–193.
- [20] H. Backman, L. Hedman, S.A. Jansson, A. Lindberg, B. Lundback, E. Ronmark, Prevalence trends in respiratory symptoms and asthma in relation to smoking – two cross-sectional studies ten years apart among adults in northern Sweden, *World Allergy Organ J.* 7 (1) (2014 Jan 2), 1–4551–7–1.
- [21] M. Lindstrom, J. Kotaniemi, E. Jonsson, B. Lundback, Smoking, respiratory symptoms, and diseases: a comparative study between northern Sweden and northern Finland: report from the FinEsS study, *Chest* 119 (3) (2001 Mar) 852–861.
- [22] H. Backman, B. Eriksson, E. Rönmark, L. Hedman, C. Stridsman, S. Jansson, et al., Decreased prevalence of moderate to severe COPD over 15 years in northern Sweden, *Respir. Med.* 22/3 (114) (2016) 103–110.
- [23] K. Warm, A. Lindberg, B. Lundback, E. Ronmark, Increase in sensitization to common airborne allergens among adults – two population-based studies 15 years apart, *Allergy Asthma Clin. Immunol.* 9 (1) (2013 Jun 11), 20–1492–9–20. eCollection 2013.
- [24] B. Lundback, L. Nystrom, L. Rosenhall, N. Stjernberg, Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey, *Eur. Respir. J.* 4 (3) (1991 Mar) 257–266.
- [25] B. Lundback, N. Stjernberg, L. Nystrom, K. Lundback, M. Lindstrom, L. Rosenhall, An interview study to estimate prevalence of asthma and chronic bronchitis. The obstructive lung disease in northern Sweden study, *Eur. J. Epidemiol.* 9 (2) (1993 Mar) 123–133.
- [26] E. Ronmark, E. Jonsson, B. Lundback, Remission of asthma in the middle aged and elderly: report from the Obstructive Lung Disease in Northern Sweden study, *Thorax* 54 (7) (1999 Jul) 611–613.
- [27] J.T. Kotaniemi, B. Lundback, M.M. Nieminen, A.R. Sovijarvi, L.A. Laitinen, Increase of asthma in adults in northern Finland?—a report from the FinEsS study, *Allergy* 56 (2) (2001 Feb) 169–174.
- [28] M. Meren, L. Jannus-Pruljan, H.M. Loit, J. Polluste, E. Jonsson, J. Kiviloog, et al., Asthma, chronic bronchitis and respiratory symptoms among adults in Estonia according to a postal questionnaire, *Respir. Med.* 95 (12) (2001 Dec) 954–964.
- [29] H.T. Lam, L. Ekerljung, N.F. Ng, E. Ronmark, K. Larsson, B. Lundback, Prevalence of COPD by disease severity in men and women in northern Vietnam, *COPD* 11 (5) (2014 Sep) 575–581.
- [30] L. Ekerljung, E. Ronmark, J. Lotvall, G. Wennergren, K. Toren, B. Lundback, Questionnaire layout and wording influence prevalence and risk estimates of respiratory symptoms in a population cohort, *Clin. Respir. J.* 7 (1) (2013 Jan) 53–63.
- [31] R. Pellegrino, G. Viegi, V. Brusasco, R.O. Crapo, F. Burgos, R. Casaburi, et al., Interpretative strategies for lung function tests, *Eur. Respir. J.* 26 (5) (2005 Nov) 948–968.
- [32] American Thoracic Society, Standardization of spirometry—1987 update. Statement of the American Thoracic Society, *Am. Rev. Respir. Dis.* 136 (5) (1987 Nov) 1285–1298.
- [33] H. Backman, A. Lindberg, A. Oden, L. Ekerljung, L. Hedman, A. Kainu, et al., Reference values for spirometry – report from the obstructive lung disease in Northern Sweden studies, *Eur. Clin. Respir. J.* 2 (2015 Jul 20), <http://dx.doi.org/10.3402/ecrj.v2.26375> eCollection 2015.
- [34] P.H. Quanjer, S. Stanojevic, T.J. Cole, X. Baur, G.L. Hall, B.H. Culver, et al., Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations, *Eur. Respir. J.* 40 (6) (2012 Dec) 1324–1343.
- [35] T. Driscoll, D.I. Nelson, K. Steenland, J. Leigh, M. Concha-Barrientos, M. Fingerhut, et al., The global burden of non-malignant respiratory disease due to occupational airborne exposures, *Am. J. Ind. Med.* 48 (6) (2005 Dec) 432–445.
- [36] I.A. Bergdahl, K. Toren, K. Eriksson, U. Hedlund, T. Nilsson, R. Flodin, et al., Increased mortality in COPD among construction workers exposed to inorganic dust, *Eur. Respir. J.* 23 (3) (2004 Mar) 402–406.
- [37] H. Backman, A. Lindberg, A. Sovijarvi, K. Larsson, B. Lundback, E. Ronmark, Evaluation of the global lung function initiative 2012 reference values for spirometry in a Swedish population sample, *BMC Pulm. Med.* 15 (2015 Mar 25), 26–015–0022–2.
- [38] J. Stocks, P.H. Quanjer, Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of the European Respiratory Society, *Eur. Respir. J.* 8 (3) (1995 Mar) 492–506.
- [39] J.A. Neder, S. Andreoni, A. Castelo-Filho, L.E. Nery, Reference values for lung function tests. I. Static volumes, *Braz J. Med. Biol. Res.* 32 (6) (1999 Jun) 703–717.
- [40] P. Paoletti, G. Viegi, L. Carrozzi, F. Di Pede, P. Modena, L. Ballerin, S. Baldacci, M. Pedreschi, G. Pistelli, C. Giuntini, Residual volume in a general population. Effects of body size, age, cigarette smoking, and respiratory symptoms, *Chest* 102 (4) (1992 Oct) 1209–1215.
- [41] E. Ronmark, A. Lundqvist, B. Lundback, L. Nystrom, Non-responders to a postal questionnaire on respiratory symptoms and diseases, *Eur. J. Epidemiol.* 15 (3) (1999 Mar) 293–299.