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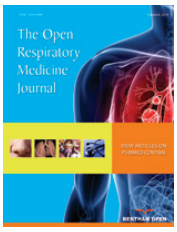

RESEARCH ARTICLE

Predicted Values for Spirometry may Underestimate Long-Standing Asthma Severity

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Abstract:

Background:

Asthma may show an accelerated lung function decline. Asthmatics, although having FEV_1 and FEV_1/VC (and z-scores) higher than the lower limit of normality, may show a significant FEV_1 decline when compared to previous measurements. We assessed how many asymptomatic long-standing asthmatics (LSA) with normal lung function showed a significant FEV_1 decline when an older FEV_1 was taken as reference point.

Methods:

46 well-controlled LSA (age: 48.8±12.1; 23 females) with normal FEV_1 and FEV_1/VC according to GLI2012 references (FEV_1: 94.8±10.1%, z-score:-0.38±0.79; FEV_1/VC: 79.3±5.2, z-score:-0.15±0.77) were selected. We considered FEV_1 decline, calculated by comparing the latest value to one at least five years older or to the highest predicted value measured at 21 years for females and 23 for males. A FEV_1 decline >15% or 30 ml/years was regarded as pathological.

Results:

When comparing the latest FEV_1 to an at least 5-year-older one (mean 8.1±1.4 years between 2 measurements), 14 subjects (30.4%) showed a FEV_1 decline <5% (mean: -2.2±2.6%), 19 (41.3%) had a FEV_1 5-15% change (mean: -9.2±2.5%) and 13 (28.3%) a FEV_1 decrease>15% (mean: -18.3±2.4). Subjects with a FEV_1 decline>30 ml/year were 28 (60.8%). When using the highest predicted FEV_1 as reference point and declines were corrected by subtracting the physiological decrease, 6 (13%) patients showed a FEV_1 decline higher than 15%, whereas asthmatics with a FEV_1 loss>30 ml/year were 17 (37%).

Conclusion:

FEV_1 decline calculation may show how severe asthma actually is, avoiding a bronchial obstruction underestimation and a possible under-treatment in lots of apparent "well-controlled" LSA with GLI2012-normal-range lung function values.

Keywords: Asthma, Lung function, Reference values, Spirometry, FEV_1 decline.

INTRODUCTION

According to guidelines, symptom severity, short-acting bronchodilator usage, disease exacerbations in the previous month and pulmonary function level set asthma treatment. Especially when spirometry values are below the predicted value normal limit, patients should be treated regularly and therapy level might be increased when necessary. This concerns also asymptomatic patients with an airway obstruction to be considered as poorly controlled. In addition, a significant peak expiratory flow (PEF) reduction >20% and/or a FEV_1 decrease ≥12%, when compared to measurements performed days/weeks/months earlier, indicate significant lung function/asthma worsening and therefore

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a treatment step-up [1, 2]. However, asthma guidelines [1] do not suggest using slower/not easily detectable FEV_1 long-term decline to establish if lung function (and therefore asthma) worsened after several years despite a good asthma control. In fact, if FEV_1, checked after inhaling bronchodilator, is compared to previous measurements (effected at least 5 years earlier) [3] and if a FEV_1 change >30 ml/year or ≥15% is found, such decrease should be regarded as pathological (airway obstruction) [2, 3]. Significant long term FEV_1 reduction/decline measurements can be considered an indirect method for assessing bronchial wall thickening and disease progression [3]. However, FEV_1 changes may be mistaken for those occurring among repeated measurements [2, 4]. Therefore, we should evaluate them by comparing such FEV_1 changes with an at least five-year-old measurement, in order not to confuse deterioration due to remodeling with the above said lung function fluctuations [3]. We know that "declining" asthmatics, whose significant irreversible airways obstruction develops over time, are approximately 20-35% of asthmatic patients. This may also regard asthmatics with pulmonary function within the predicted normal range if their latest "normal" lung function is compared with an at least five-year-old higher measurement. This apparent "normality" is due to a yearly predicted reference reduction that may hide a possible lung function decline due to asthma, leading to an underestimation of airflow limitation [3, 5]. In fact, pulmonary function might be within the predicted normal range despite a significant lung function decline. The absence of symptoms in such patients might lead to an undervaluation of asthma severity [3]. This is why it may be important to compare the latest spirometry with at least a five-year-old one when managing asthma. Nowadays, we do not know how many "well controlled" long acting asthmatics, with apparent lung function normality, can actually show an accelerated FEV_1 decline, leading to an evaluation bias.

Recently, the Global Lungs Initiative (GLI) 2012 has made available spirometric prediction equations for the 3–95 age range, including appropriate age-dependent lower limits of normal [6 - 8]. Adopting GLI 2012 prediction equations will have little effect on the detection of obstructive patterns when compared to previous NHANES and ECSC/ERS equations.

On the basis of these considerations, objective of this study was to establish the number of subjects that showed a significant FEV_1 decline in a group of asthmatics with normal lung function in the latest assessment, according to GLI2012 references. Furthermore, we wanted to know the number of subjects with significant FEV_1 changes in time, taking as reference points the highest predicted values measured at 21 years for females and 23 for males, (when these references are higher) in order to calculate such decline.

PATIENTS AND METHODS

We selected and retrospectively analyzed 46 consecutive long-standing asthmatics from our outpatient database (mean age: 48.8±12.1; 23 females, 4 current smokers; 40 sensitized at least to one aero-allergen). They all had normal lung function, in particular FEV_1 and FEV_1/VC greater than the LLN, with their z-score between -1.5 and 1.5, calculated by using GLI equations) [6 - 8] (FEV_1: 94.8±10.1%, z-score: -0.38±0.79; FEV_1/VC:79.3±5.2, z-score: -0.15±0.77). They all had also a clinical stable disease at least in the previous 6 months with an Asthma Control Test (ACT) score >20 at the time of the latest assessment. Pulmonary function data, aero-allergenic sensitization to prick tests, exacerbation rates (defined by the use of systemic corticosteroid and/or emergency room accesses), ACT score, treatment and adherence, were taken from the medical record of each patient. For the purpose of this study, all patients' FEV_1 and FEV_1/VC measurements with their z-scores - measured after bronchodilator (Salbutamol) at the start and at the end of at least a 5-year period of time - were considered. Previous FEV_1 and FEV_1/VC values (and their z-scores) measured at least 5 years before the latest measurement and the highest predicted FEV_1 values (obtained at 21/23 years for females and males respectively) were considered as reference points to calculate FEV_1 decline for each patient. Therefore, absolute (ml) and percentage changes between the latest and the oldest FEV_1 and between the latest FEV_1 value and the highest predicted FEV_1 values, were taken into account.

Annual FEV_1 changes obtained for each patient were expressed in ml/year. When the oldest FEV_1 value was used as reference point, FEV_1 change was calculated by subtracting the latest measured value from the oldest FEV_1, [($FEV_{1\ previous}$ – $FEV_{1\ latest}$)/years] and then subdivided by the years separating the two measurements. When the reference point was the highest FEV_1 predicted value, the variation was calculated by subtracting the latest measured value from the highest

FEV_1 predicted value, [($FEV_{1\ highest\ predicted}$ − $FEV_{1\ latest}$)/years], when it is usually higher. This value was then subdivided by the years separating the two measurements. Percentage change was calculated by subtracting the previous absolute measurement or the highest predicted values (expressed in ml) from the latest measurement and then divided by the previous or the highest predicted measurements *100: [($FEV_{1\ previous}$ − $FEV_{1\ latest}$)/ $FEV_{1\ old}$]*100 and [($FEV_{1\ highest\ predicted}$ − $FEV_{1\ latest}$) / $FEV_{1\ highest\ predicted}$]*100. We also calculated physiological annual FEV_1 decline, according to GLI2012, by subtracting the predicted value of the latest measurement from the highest predicted FEV_1 value, and then by subdividing by the years elapsed between the two measurements: [($FEV_{1\ highest\ predicted}$ − $FEV_{1\ latest\ predicted}$)/years]. The physiological change percentage was calculated by using the following formula: [($FEV_{1\ highest\ predicted}$ − $FEV_{1\ latest\ predicted}$)/ $FEV_{1\ highest\ predicted}$]*100.

Arbitrarily, on the basis of a FEV_1 decrease <5%, or 5-15% or >15%, obtained between the oldest and the latest measurements, patients were subdivided into three groups, Also an annual FEV_1 change < 30, 30-60 and > 60 ml/year was used to calculate the prevalence of subjects with different FEV_1 declines expressed in ml/year. When the reference point was the highest predicted FEV_1, the percentage changes from the latest measurement were higher as the years separating the two measurements were more numerous, above all in subjects of medium/old age. Therefore, to correct the bias, FEV_1% decline was calculated by using the above mentioned formulas, but subtracting physiological FEV_1 decline measured between the two normal predicted values (highest predicted FEV_1 and predicted value of the latest measured FEV_1). For this reason, the corrected formula was: [($FEV_{1\ highest\ predicted}$ − $FEV_{1\ latest}$) − ($FEV_{1\ highest\ predicted}$ − $FEV_{1\ latest\ predicted}$) / $FEV_{1\ highest\ predicted}$]*100. All functional data of formulas were considered in liters. A FEV_1 decrease in time, greater than 15% or 30 ml/years for each patient, compared to one of their previous highest FEV_1 measurements and to their highest predicted value (having removed physiological FEV_1 decline when using cut-off percentage) was considered expressive of pathological long term FEV_1 decline. All subjects had been treated with low/medium doses of inhaled corticosteroids, sometimes associated to long-acting bronchodilators and montelukast. The asthma diagnosis was made by the methacholine test and/or reversibility test or after an exacerbation of the disease. Initial and final FEV_1 and FVC measurements should be <12% increase after salbutamol.

The retrospective use of data for this study was approved by the local ethical Committee (Prot. 178/25-09-2012).

STATISTICAL ANALYSIS

Unpaired and paired ANOVA tests were used, when appropriate, to compare functional parameters among different groups. A χ^2 test was used to compare the prevalence of subjects with different FEV_1 declines.

RESULTS

In Table **1** are summarized spirometric measurements obtained in the three groups with low (<5%), medium (5-15%) and high (>15%) FEV_1 decline. Obviously, in groups with a greater lung function dceline, the oldest and latest parameters were different (Table **1**). When we considered the highest predicted or older values as reference to calculate their FEV_1% and z-score, the first and the last measurements were similar in the group with a 5% FEV_1 long-term change, but not in the groups with 5-10% and >15% decrease (Table **1**).

Table 1. Mean values of lung function measured in the 3 groups of long-standing asthmatics with different FEV_1 decline.

	Asthmatics with FEV_1 long-term change ≤5% (14 subjects)			**Asthmatics with FEV_1 long-term change between 5 and 15% (19 subjects)**			**Asthmatics with FEV_1 long-term change >15% (13 subjects)**		
	Previous measurement	**Latest measurement**	**p**	**Previous measurement**	**Latest measurement**	**p**	**Previous measurement**	**Latest measurement**	**p**
FEV_1 L	3.36±0.88	3.3±0.9	0.412	3.18±0.72	2.9±0.7	<0.01	3.55±0.7	2.91±0.62	<0.001
$FEV_{1\%}$	96.74±9.34	101.17±10.75	<0.001	95.34±9.58	92.1±9.01	<0.001	105.1±9.34*	91.26±8.15°	<0.001
z-score FEV_1	-0.24±0.76	0.11±0.87	<0.001	-0.36±0.78	-0.58±0.71	<0.001	0.42±0.74	-0.64±0.6	<0.001
FEV_1/VC	81.14±5.99	80.35±5.78	0.458	81.73±5.3	80.21±5.28	0.076	81.6±4.85	76.92±3.79	<0.001
z-score FEV_1/VC	-0.23±0.78	-0.06±0.79	0.344	0.01±0.72	-0.01±0.78	0.870	0.06±0.77	-0.46±0.70	0.002

(Table 1) contd.....

	Asthmatics with FEV_1 long-term change ≤5% (14 subjects)			Asthmatics with FEV_1 long-term change between 5 and 15% (19 subjects)			Asthmatics with FEV_1 long-term change >15% (13 subjects)		
	Previous measurement	**Latest measurement**	**p**	**Previous measurement**	**Latest measurement**	**p**	**Previous measurement**	**Latest measurement**	**p**
FEV_1% (of the highest predicted value)	85.85±13.55	84.2±15	0.015	84.6±9.6	74±19.6	0.006	90.2±11.9	73.5±10.1	<0.001
z-score FEV_1 (of the highest predicted value)	-1.19±1.14	-1.33±1.26	0.017	-1.25±0.87	-1.91±0.79	<0.001	-0,83±1.01	-2,25±0,85	<0.001
FEV_1% (of the previous value)	100	97.8±2.68	0.009	100	90.7±2.52	<0.001	100	81.85±2.47$^{\#}$	<0.001
z-score FEV_1 (of the previous value)	0	-0.14±0.20	0.021	0	-0.7±0.18	<0.001	0	-1.41±0.25$^{\#}$	<0.001

FEV_1 % of the highest predicted values: the highest predicted FEV_1 obtained at 21 years for females and 23 years for males was used as reference point to calculate the percentage value of the previous ($FEV_{1previous}/FEV_{1highest\ predicted}$*100) and the latest ($FEV_{1latest}/FEV_{1highest\ predicted}$*100) measurements expressed in percentage.

Z-score FEV_1 (of the highest predicted values): z-scores mean values of FEV_1 % (of the highest predicted values).

FEV_1 % of the previous values: the previous FEV_1 was used as reference to calculate the percentage value of the previous ($FEV_{1previous}/FEV_{1previous}$*100) and the latest ($FEV_{1latest}/FEV_{1previous}$*100) measurements expressed in percentage.

Z-score FEV_1 (of the previous predicted values): z-score mean values of FEV_1 % (of the previous values).

*comparisons with previous measurements of other groups, p=0.017; $^{\circ}$comparisons with latest measurements of other groups, p=0.012; $^{\#}$comparisons with latest measurements of other groups, p<0.001.

Paired and unpaired ANOVA tests were used when appropriated.

The time that separated the previous measurements from the latest ones were similar (8.3±1.5, 7.8±1.2 and 8.3±1.6 years in subjects with low, medium and high FEV_1 decline respectively). Also the time between the highest predicted and latest measurements was similar (Table **2**). Obviously, the FEV_1 decline from the oldest value, both expressed in ml/year and percentage was different in the 3 groups (Table **2**). Mean values of the highest predicted FEV_1 were 3.88±0.65, 3.73±0.56 and 3.9±0.7 liters in subjects with low, medium and high FEV_1 decline respectively. When the highest predicted FEV_1 was used as reference point, FEV_1 changes were different among three groups (Table **2**). Physiological FEV_1 decline (calculated by the difference between the highest predicted FEV_1 and the predicted value of the latest measurement), both expressed in ml/year and percentage, were similar in all groups (Table **2**).

Table 2. FEV_1 decline calculated by subtracting the latest measurement from the previous one or from the highest predicted value. The table shows also the time that separates the latest measurement from the reference points in the 3 groups of long-standing asthmatics with different FEV_1 declines.

	Asthmatics with FEV_1 long-term change ≤5% (14 subjects)	Asthmatics with FEV_1 long-term change between 5 and 15% (19 subjects)	Asthmatics with FEV_1 long-term change >15% (13 subjects)	p
ΔFEV_1 (ml/year) between the previous and the latest measurements	-7.7±12.4	-37.1±9.3	-80.3±20.3	<0.001
ΔFEV_1 (%) between the previous and the latest measurements	-2.2±2.6	-9.2±2.5	-18.3±2.4	<0.001
Time between the previous and the latest measurements (years)	8.28±1.54	7.8±1.22	8.3±1.6	0.1
ΔFEV_1 (%) between the highest predicted value and the latest measurement	-15.8±15.6	-23±9.7	-25.9±11.3	0.025
ΔFEV_1 (%) between the highest predicted value and the latest measurement (corrected by physiological decline)	-1.92±6.88	-7.03±6.08	-8.2±8.5	0.02

(Table 2) contd.....

	Asthmatics with FEV_1 long-term change ≤5% (14 subjects)	Asthmatics with FEV_1 long-term change between 5 and 15% (19 subjects)	Asthmatics with FEV_1 long-term change >15% (13 subjects)	p
ΔFEV$_1$ (ml/year) between the highest predicted and the latest values	-20.6±40.2	31.3±9.7	33.12±12.7	0.04
Time between the highest predicted and the latest measurements (years)	29±10	26.84±9.25	24.85±17.35	0.1
Physiological Δ FEV$_1$ (ml/year) (between the highest predicted and the latest predicted measurements)	-21.2±4.2	-21.51±3.34	-22.76±5	0.3
Physiological Δ FEV$_1$ (%) between the highest predicted and the latest predicted measurements)	-15.17±12.5	-13.55±10.7	-17.1±7.26	0.09

See materials and methods for formulas used to calculate the various FEV_1 declines. Comparisons were made by using ANOVA test.

Thirteen patients (28.3%; mean age: 50.1±10.1) highlighted a significant FEV_1 decline higher than 15% in comparison to an older FEV_1 (Fig. (**1A**)), even though their latest FEV_1 and FEV_1/VC were higher than the GLI2012 low limit of normality and their z-score > -1.5 (see Table **1** for mean values). The prevalence of subjects with long term FEV_1 decrease <5% were 14 (30.4%; mean age: 46.85±17), whereas those with FEV_1 5-15% change resulted to be 19 (41.3%; mean age: 48.6±8.9) (Fig. (**1A**)). The prevalence of subjects with a decrease <30, 30-60 and >60 ml/year, calculated by the formula [($FEV_{1\ previous}$ – $FEV_{1\ latest}$)/years], was 39, 37 and 24% respectively (Fig. (**1B**)). When the highest predicted value was used as reference point, and the reduction was corrected by subtracting the physiological decline, 6 (13%) patients showed a FEV_1 decrease higher than 15% (Fig. (**2A**)). Subjects with a FEV_1 change >30 ml/year, compared to the highest predicted values ([($FEV_{1\ highest\ predicted}$ – $FEV_{1\ latest}$)/years]), were 17 (36.9%) (Fig. (**2B**)).

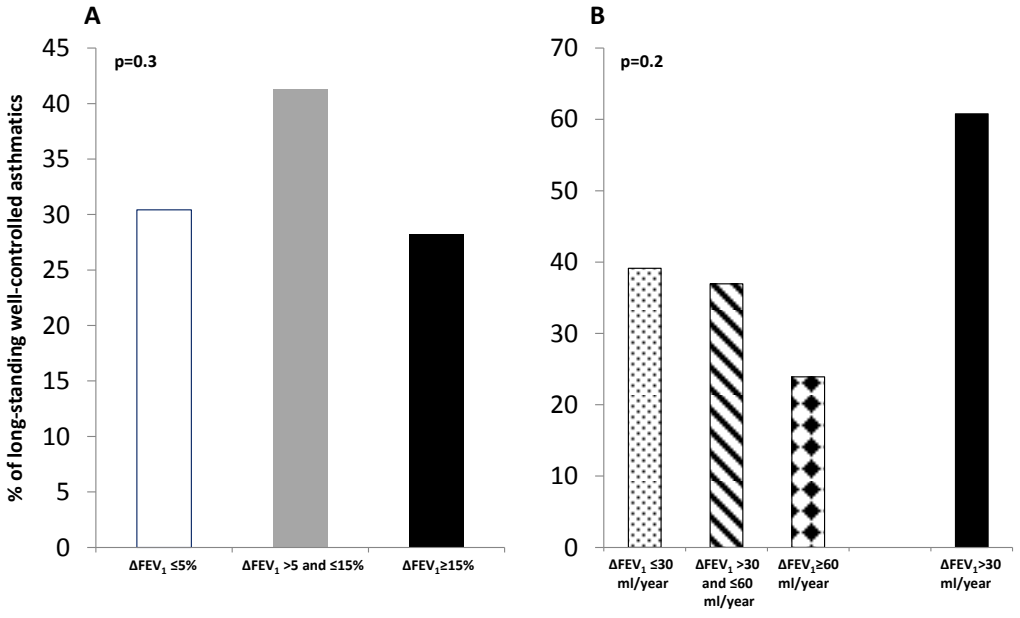

Fig. (1). Prevalence of long-standing asthmatics with different FEV_1 declines calculated by subtracting the latest measurement from a previous one. **A:** FEV_1 decline expressed in percentage; **B:** FEV1 decline expressed in ml/year.
See materials and methods for formulas used to calculate the various FEV1 declines. Comparisons were made by using χ^2 test.

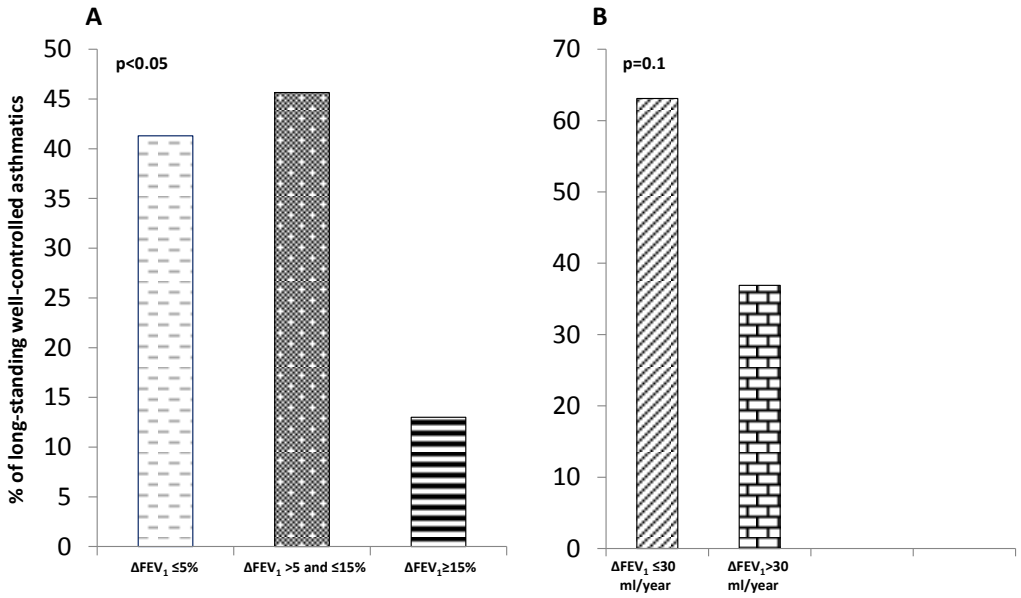

Fig. (2). Prevalence of long-standing asthmatics with different FEV_1 declines calculated by subtracting the latest measurements from the highest predicted value (measured at 21 years for females and 23 years for males), used as reference point. **A:** FEV_1 decline expressed in percentage (corrected by subtracting the physiological FEV_1 decline); **B:** FEV_1 decline expressed in ml/year.
See materials and methods for formulas used to calculate the various FEV1 declines. Comparisons were made by using χ^2 test.

DISCUSSION

As highlighted by this study, approximately 28% of well-controlled asthmatics showed a significant FEV_1 decline (>15%) when compared to an approximately 8-year earlier measurement, despite their latest FEV_1 and FEV_1/VC (and z-scores) were normal, greater than the LLN (according to GLI2012). The percentage of subjects with "normal" lung function, but with a significant FEV_1 decline rose to 60% when a cut-off >30ml/year was used to define a pathological limit of long-term FEV_1 change [2, 3]. Therefore, this accelerated lung function deterioration might regard a remarkable number of subjects with "normal" pulmonary function that would remain undiagnosed without a comparison with a previous spirometry. Identification of "declining" asthmatics may indicate that they are either steroid-resistant or inadequately treated because they are either under-perceivers or poorly adherent to therapy. They may also be unable to use devices properly or have an inadequate lifestyle. We should also consider greater noxious environmental exposure (allergens, smoking habits, working exposure, air pollution, etc.) and other associated diseases (rhinitis, gastro-esophageal reflux, etc.) that may influence lung function deterioration [3].

The three different FEV_1 decline levels identified in this population of treated long-standing asthmatics are perfectly in line with what was found in another study conducted on asthmatics assessed after 5, 10 and 15 years [9], that showed a FEV_1 decline of <60 ml and >60 ml in 35–60% and 20–35% of patients respectively, whereas no change were observed in 10–25% of them. These different severities of FEV_1 decline may identify distinct asthma phenotypes with dissimilar responses to anti-inflammatory therapies. In fact, different levels of lung function decline may be simply due to diverse inflammatory patterns characterizing asthmatics: Th2, Th2/17 and Th17. These phenotypes may have no/scarce, moderate and severe FEV_1 decline respectively, that may be associated with an inverse response to anti-inflammatory treatment [10, 11]. Therefore, it is also likely that a different severity of decline (mild–moderate or severe), in well treated asthmatics, may be a marker that would allow identifying 'responsive' and 'non-responsive' subjects to treatment and therefore those with more severe asthma.

As already stated, according to this study, a latest measured value within normal range of references (>LLN) may

lead us to an incorrect evaluation of long-standing asthmatics. In fact, such "normal" values might lead to an underestimation of bronchial obstruction and therefore asthma severity, if we do not make a comparison with an at least 5-year-old spirometry. This apparent normality is due to the annual physiological reduction of normal range references (including the ones proposed by GLI2012) [6 - 8] that may hide a significant lung function decrease in time. In fact, normal predicted values and low limit of normal (LLN) increase until the age of 21-23 and then decrease in the following years, even though height (used to calculate predicted values) remains unchanged [6 - 8]. This progressive reference value reduction with age may conceal a significant functional deterioration due to asthma airway remodeling. Besides, low limit of normal (LLN) (also decreasing with age) may be lower than the predicted value of approximately 20% or more (700-800 ml). Such a large normality range may falsely lead to consider a low (but higher than LLN) FEV_1 measured value as normal, in case we have no past functional reference measurements. Consequently, percentage values calculated from the predicted and their z scores, obtained in two measurements effected at a distance of years, may be approximately similar and higher than LLN values, which consequently result normal. Changes in predicted values may be excessive for some asthmatics over the course of time: lung function was and remained normal despite its significant decline in time. Therefore, asthma-induced lung function decline may be unchecked if it is higher than the physiological reduction of predicted lower limit of normality. This may regard especially younger subjects showing high lung function values at asthma onset, much higher than normal references, and that during the following years are characterized by a moderate asthma FEV_1 decline (between 30-80 ml/year). Their predicted and LLN values may be unable to detect these significant variations occurring during a long period of time, as it has been observed in some patients in this study. An early decrease of normal predicted and LLN values, starting after 21-23 years of age, might explain such erroneous assessment. In our opinion, reference values should begin to decrease later. Likely, such values should reach their peak at the above said age (due to growth). Later, we suppose they should remain constant in time (at least in some subjects to be identified) or decrease more slowly until the age of 35 (or later) and then begin to decrease physiologically. In fact, observing the distribution of healthy subjects with normal/high values of pulmonary function, we can see that this remains unchanged in a remarkable number of 20-40 age-bracket individuals [7]. Therefore, not all subjects seem to show a physiological lung function decline during youth. Even asthmatics may not report any lung function deterioration. In fact, approximately 30% of our asthmatics showed that their lung function remains unchanged in time, when compared to older measurement. Furthermore, several factors may influence loss in pulmonary function which is not evaluated in healthy subjects taken into consideration for population lung function references. For example, air pollution, workplace exposure, fat diet and obesity can affect lung function decline [3]. In addition, the presence of most respiratory diseases was excluded only by a questionnaire during the recruitment of reference population samples. In fact, also other respiratory diseases (COPD, interstitial diseases, and occupational exposure damages) can show lung function deterioration in time.

Often, when we manage long-standing asthmatics, we might not have an old spirometry and therefore we might not have a reference point to calculate FEV_1 decline. The "highest predicted FEV_1 value" (measured at 21 years for females and 23 years for males) may be a valid alternative, as a fixed point of reference, instead of a previous FEV_1 value". In fact, using this reference point, reduced by subtracting the physiological change in time, (i.e. $[(FEV_{1\ highest\ predicted} - FEV_{1\ latest}) - (FEV_{1\ highest\ predicted} - FEV_{1\ latest\ predicted}) / FEV_{1\ highest\ predicted}]*100$) we found that 6 (13%) patients showed a significant FEV_1 decline (higher than 15%) showing that these patients were really affected by airway obstruction. Subjects with an accelerated lung function decline became 17 (36.9%) in case we used a FEV_1 change in time >30 ml/year (compared to the highest predicted) as a significant long-term decrease cut-off. If we had these long-term changes available on each spirometry (automatically calculated), we could have reference values that might allow considering asthma airway remodeling on lung function. A fixed reference point could therefore permit to calculate FEV_1 decline (to be shown in spirometry reports) which may improve asthma monitoring and give spirometry a different role. Fixed "highest" values, taken as reference values, may give a "dynamic" vision in time, whereas "FEV_1 predicted value", reducing with age, gives only a "static" asthma evaluation only at a specific moment in time.

We retain that FEV_1 decline should always be considered because it allows evaluating the real impact of asthma on long-standing asthmatics more correctly, otherwise they would be erroneously considered as well controlled. This evaluation of pulmonary function decline is currently performed for workers with the purpose of screening possible pulmonary damages caused by occupational exposure (asbestos, coke oven emissions, cadmium, cotton dust, benzene, formaldehyde etc) [5]. Since asthma is due to allergen-exposure causing inflammation-induced airway remodeling [1, 3], and thus lung function decline, a long-term monitoring should be also considered in asthma, in order to establish treatment efficacy, despite a good symptom control [3]. Therefore, as already stated, despite a good symptom control,

identifying declining asthmatics may allow us to make some treatment adjustments, i.e. improving adherence and /or increasing inhaled corticosteroid doses when they are particularly low. In fact, long-term clinical trials have shown that inhaled corticosteroids can slow down lung function decline in asthma [12 - 16]. In particular, an early treatment with inhaled corticosteroids can reduce FEV_1 loss more significantly [12, 16]. Furthermore, it may be advisable to reduce harmful environmental exposure and improve lifestyle in order to contrast lung function deterioration in time [3]. In fact, some studies have shown that weight reduction may be beneficial on asthma outcomes and above on all lung function decline [17, 18].

However, it must be underlined that, when evaluating changes between two measurements (at a distance of several years), variability of FEV_1 in repeated measurements should be considered [2 - 4]. Therefore, it is advisable to calculate FEV_1 decline considering the FEV_1 values obtained after using a bronchodilator. Furthermore, lung function decline evaluation should be supported by some intermediate, progressively decreasing measurements (between the first and the last spirometries) in order to confirm deterioration in time.

CONCLUSION

In approximately 28% of asymptomatic long-standing asthmatics, if their latest lung functional value within reference normal range is compared with one at least 5 years older, we can see a significant pulmonary function decline (>15%). The apparent "normality" of the latest measurement may lead us to an underestimation of asthma severity in these asthmatics. This bias is due to a physiological reduction of reference values for spirometry with age that can hide an asthma-induced lung function decline (remodeling). The highest predicted value obtained at the age of 21 years for females and 23 years for males may be used as fixed reference point, alternatively to a previous FEV_1 measured at least five years earlier, to calculate FEV_1 decline. In subjects with "normal" lung function, availability of the FEV_1 decline measurement on the report of spirometry, either from previous or from the highest predicted values, may allow us to see how severe their asthma is despite the absence of symptoms and, consequently, lead to a better disease management. Obviously, further studies should be necessary to validate this approach to asthma.

CONFLICT OF INTEREST

The author declares that they have no conflicts of interest in relation to this article.

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DISCLOSURE

Dr. B. Sposato, as the main researcher, is responsible for the conception and design of the article as well as interpretation, analysis and writing.

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