Sensitivity of FEV1 and Clinical Parameters in Children With a Suspected Asthma Diagnosis

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ABSTRACT (282 words)

Backgroud: Asthma is the most common chronic disease in children and a robust diagnosis is crucial to optimize patient care and reduce its burden. To diagnose asthma in children, GINA recommendations propose a 12% improvement in FEV_1 after a bronchodilation test. Nevertheless, such criterion is rarely confirmed in these patients in clinical practice.

Objective: The objective of this study was to evaluate the sensitivity of spirometric and clinical parameters in identifying children with possible asthma.

Methods: The VERI-VEMS Study is a multicenter international retrospective cohort study. Data were collected, from January 2008 until January 2019, for all consecutive children (aged 5 to 18 years), with a diagnosis of asthma, who performed a spirometry at the time of the diagnosis. We compared the sensitivity of the reversibility criterion proposed by GINA guidelines, with other spirometric and clinical variables, using physician diagnosed asthma and response to treatment as the standard.

Results: 871 children were included in the study. The reversibility criterion of 12% of FEV_1 showed a sensitivity of 30.4%. The three best spirometric or clinical criteria were the presence of "dry cough, or wheezing or atopy" and "dry cough, or wheezing or exercise induced dyspnea", with a sensitivity reaching 99.5%, with no added value of the spirometric parameters in the calculation of the culmulated sensitivity for the diagnosis of pediatric asthma.

Conclusion: Post bronchodilator reversibility of 12%, although essential for patients' follow-up, has an insufficient low sensitivity in reaching a diagnosis of asthma in pediatric patients, compared to a combination of clinical symptoms, that show, on the other hand, a better sensitivity. Further studies on specificity will help clarify the role of this change in diagnostic paradigm in formally diagnosing children with asthma.

Trial Registration The study was registered on ClinicalTrials.gov (ID: NCT03814018).

58 **Keywords**: asthma; children; Pulmunary Function Tests; FEV_1; clinical symptoms; GINA;
59 sensitivity.

60

Highlights box

1. What is already known about this topic?
    - GINA international guidelines advise to perform pulmonary function tests to diagnose asthma, both in children and adults. Diagnostic criteria in children require a FEV_1/FVC ratio lower than 90% and an increase of 12% of their FEV_1 after bronchodilation test, based on what was observed in adults.
2. What does this article add to our knowledge?
    - In this multicenter international retrospective cohort study, we evaluated pulmonary function tests results of children with a physician-made diagnosis of asthma, and collected clinical data, to assess the sensitivity of the FEV_1 reversibility criterion. While reversibility criteria showed a sensitivity of 30.4%, the sensivitity of the association of three clinical parameters was 99.5%.
3. How does this study impact current management guidelines?
    - The results of the present work bring an important contribution to current knowledge on asthma diagnosis in children, showing that spirometric values have a very unsatisfying low sensitivity, especially if compared with clinical symptoms.

Abbreviations

AIT – Allergen Immunotherapy

FEF_{25-75} – Forced expiratory flow at 25-75% of the pulmonary volume
F_ENO – Fractional exhaled nitric oxide
FEV_1 – Forced Expiratory Volume in 1 second
FVC – Forced vital capacity
GINA – Global Initiative for Asthma

PFTs – Pulmonary Function Tests

SD – Standard Deviation

Se – Sensitivity

Introduction

Asthma is a chronic inflammatory disorder of the bronchi, associated to airflow hyper-reactivity, and possibly leading to acute symptoms, that are reversible either spontaneously or after appropriate bronchodilator treatment[1,2]. With both prevalence and incidence increasing over the last decades, asthma is a major public health problem[3-5]. Considering the pediatric population, asthma is the most frequent chronic non-communicable disease, and the leading cause of childhood morbidity, mainly caused by acute exacerbations characterized by breathlessness, wheezing, chest tightness, and/or cough[6,7]. It is also associated to a high rate of emergency room visits, hospitalizations, absenteism from school and presenteism, and still contributes to many deaths amongst young people even in developed countries[2,8]. This condition, also frequent in adulthood, often begins in early childhood, with an earlier onset in males, and initially with intermittent symptoms, especially occurring during viral respiratory tract infections. Other possible triggers include allergies, physical exercise, cold air, extreme emotional arousal, and even some drugs (aspirin, non-steroid anti-inflammatory drugs, or beta-blockers)[3,9,10]. In pediatrics, known predisposition factors include a family history of asthma, atopy, allergic rhinitis, low birth weight or a history of multiple wheezing episodes during the first two years of life[11-15]. In general, asthma is known to be a chronic disease, tending to present as a lifetime condition[16,17]. For such reason, an appropriate management with a correct and prompt diagnosis is crucial to control symptoms and therefore reduce asthma burden and increase patients' quality of life. The Global Initiative for Asthma (GINA) international guidelines advise to perform pulmonary function tests (PFTs) to diagnose asthma, both in children and adults. Diagnostic criteria in children require a FEV_1/FVC ratio lower than 90% and an increase of 12% of their FEV_1 after bronchodilation test, based on what was observed in adults[4,18-20]. Nevertheless, the bronchodilation test following GINA recommendations, is sometimes difficult to perform in children younger than 5 years, due to age-related difficulties in achieving test-satisfying controlled expirations[4,12,21,22]. The increase of the FEF_{25-75} after bronchodilation has also been proposed in children to corroborate the diagnosis, but studies seem not to be conclusive[23,24]. Also,

114 the accuracy of these criteria is debated in children and other possible diagnostic methods have been
115 investigated[25,26]. Indeed, in clinical practice, clinical signs and response to inhaled therapy are
116 currently considered by pediatricians as the most useful tools to suspect and then diagnose asthma
117 in children[27,28].

118 The aim of the present study was to measure, in real-life settings, the sensitivity of the
119 reversibility criterion proposed by GINA recommendations (i.e., the increase of 12% of the FEV_1),
120 and to look for other spirometric and clinical parameters with a high sensitivity to identify children
121 that respond to asthma treatment, and that may be appropriate to clinical management, without
122 further testing, for a diagnosis of asthma in children.

Methods

1. Study Design and included population

We conducted a multicenter retrospective cohort study that included data from January 2008 to January 2019. Data were collected at the Pediatric and at the Allergy Unit of the University Hospital of Montpellier, France, and at the Immunology and Allergy Pediatric Unit of the University Hospital of Pavia, Italy. The study was approved by a local ethical committee, in Montpellier (2019_IRB-MTP_01-06) and validated by the Ethical Committee of the University Hospital of Pavia. The study was registered on ClinicalTrials.gov (ID: NCT03814018).

We included all consecutive children, followed by each center, with a diagnosis of asthma, and who performed a PFT at the time of the diagnosis. In each center, patients were considered as asthmatic if, after the first consultation, the pediatrician, specialized in childhood respiratory and allergic diseases, concluded the visit by declaring the child affected by asthma, and if they responded to prescribed treatment at least within 2 follow-up visits. This was clearly based on their long clinical experience, including PFT results and response to anti-asthma treatments. Diagnosis of asthma had to be reached between their 5^{th} and their 18^{th} anniversary. Children were excluded if suffering from other chronic and obstructive respiratory diseases, acute infectious diseases, and genetic disorders possible affecting the respiratory system. They were also excluded if, at the time of the first visit, they had already been prescribed with anti-asthmatic drugs, including short-acting beta agonists, inhaled corticosteroids, and leukotriene receptor antagonists. They were also excluded if PFTs results didn't meet acceptability criteria.

For each patient, we collected demographic information (height, weight, age at diagnosis, sex), country of provenance (either France or Italy), PFT results at the time of the diagnosis, asthma severity (based on prescribed treatment and GINA guidelines), clinical information (presented symptoms, physician-evaluated treatment efficacy after the first consultation, personal history of bronchiolitis/recurrent wheezing during the first two years of life). Presence of atopic comorbidities was evaluated as well, including atopy, defined as sensitization to at least one common respiratory

allergen (including *Dermatophagoides pteronissinus*, *Dermatophagoides farinae*, grass, cypress, birch, cat, dog, *Alternaria alternata*); allergic rhinitis, defined as the presence of typical disease symptoms due to exposure to an airborne allergen to which the patients are sensitized; food allergy, defined as the appearance of hypersensitivity symptoms related to consumption of a food allergen to which the patients are sensitized, or a positive food challenge to the culprit food; atopic dermatitis, defined by the presence of an inflammatory, pruritic, chronic or chronically relapsing skin disease, and on the recognition of characteristic signs and symptoms by a pediatric allergist[29].

2. *Outcomes of the study*

The primary outcome of this study was to assess the sensitivity of the reversibility criterion proposed by GINA guidelines of an increase of 12% of FEV_1 after bronchodilation test, compared to clinical symptoms that respond to therapy to diagnose presumed pediatric asthma.

The secondary endpoints were: (i) to assess the sensitivity of other spirometric parameters – such as the presence of obstructive syndrome in children, as proposed by GINA guidelines ($FEV_1/FVC < 90\%$), and the reversibility of small airways (FEF_{25-75}), defined as an increase greater than 30% after bronchodilation test from basal values; and (ii) to evaluate, in a subgroups analysis, possible correlations between asthma severity and comorbidities.

3. *Statistical analysis*

Continuous variables were summarized with descriptive statistics (number, mean, SD), while frequency counts and percentages were provided for categorical data. Statistics were computed for patients with available (i.e., non-missing) data. Comparison of patient characteristics was assessed after grouping patients as for asthma severity (persistent severe, persistent moderate, persistent mild, and intermittent asthma). We used the Student's *t*-test for data in case of continuous variables and the chi-square test for categorical variables. Differences between groups were considered statistically significant if *p*-values were <0.05.

All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA).

Results

1. *Included population*

We included a total of 888 children with a diagnosis of asthma reached between January 2008 and January 2019. 17 of them were excluded from the analysis because of missing data (Figure 1). 342 patients were included from the Montpellier University Hospital: 219 of them (64.0%) were males; their mean age at diagnosis was 9.2 years (SD 3.4). 529 patients were included from the Pavia University Hospital: 329 of them (62.2%) were males; their mean age at diagnosis was 9.3 years (SD 3.2). The two populations were not statistically different, when considering their sex and their age (*p-value*: 0.5825 and 0.6605, respectively). Moreover, basal FEV_1 values did not differ between the French and Italian population (1800 mL and 1900 mL, respectively; *p-value*: 0.0728). For all the above reasons, statistical analysis was performed considering the two groups as a single cohort. On the other hand, since there was a significant difference between mean basal values of FEV_1/FVC in the two populations and the presence of atopy, allergic rhinitis, and food allergy, we also assessed the sensitivity of spirometric criteria in the two countries, separately (*vide infra*).

An interesting difference between the two populations concerned the prescription of Allergen Immunotherapy (AIT): patients received significantly more AIT treatments in the French population, compared with the Italian one (17.0% vs. 8.1%; *p-value* < 0.0001). Another difference concerned sensitization to cypress and birch pollen: in fact, cypress pollen allergy is very common in the Montpellier area, but not in the Pavia area. The opposite consideration is true for birch pollen allergy. We considered these differences very unlikely to influence our objectives.

Characteristics of the children included in the study are shown in Table 1.

2. *Primary outcome*

The reversibility criterion of an increase of at least 12% of the FEV_1 after bronchodilation test was confirmed in 266 out of 871 children (Figure 2), with a sensitivity (Se) of 30.4% (Table 2).

When considering children with a $FEV_1/FVC < 90\%$, the reversibility criterion showed a 23.5% sensitivity, being recorded in 205 children only. There was no significant difference between the two centers (31.0% and 30.1% sensitivity in the French and Italian population, respectively). Moreover, the mean change in FEV_1 after bronchodilation was similar in the two centers as well (8.1% with 13.1% of SD, and 8.3% with 8.8% of SD, respectively; *p-value*: 0.79).

3. Obstruction criterion and small airways criterion

The obstruction criterion proposed by GINA guidelines for children ($FEV_1/FVC < 90\%$) was confirmed in 595 children, with a sensitivity of 67.5% overall (Table 2). The mean value of the FEV_1/FVC ratio in the entire cohort was 85% (SD 10%).

The increase of more than 30% in FEF_{25-75} after bronchodilation test was only found in 198 children in our cohort (Se 21.9%), with a mean value of 22.1% (SD 30.0%) (Table 2). Furthermore, older children (>11 years group) were also less likely to achieve this reversibility criterion, compared with patients with less than 7 years of age, or between 7 and 11 years (15.1%, 24.9%, and 23.8%, respectively).

4. Most sensitive criteria to identify presumed asthma

To assess the variables providing the best sensitivity to identify presumed asthma, we included in the analysis both the spirometric criteria ($FEV_1/FVC < 90\%$, change in $FEV_1 > 12\%$, change in $FEF_{25-75} > 30\%$), and the clinical ones (dry cough, tight chest, wheezing, pre-school wheezing, exercise-induced dyspnea, atopy, presence of allergic comorbidities). The best single criterion was the presence of ″dry cough" (Se 90.9%). Sensitivity of each criterion is shown in Table 3. The best two combined criteria were "dry cough or atopy" (Se 98.5%), followed by both "dry cough or wheezing" or "dry cough or allergic comorbidities" (Se of 97.7%).

Furthermore, the best three criteria to identify presumed asthma were "dry cough, or

wheezing or atopy", and "dry cough, or wheezing or exercise-induced dyspnea", with both a sensitivity of 99.5%. The combination of the previously mentioned four criteria (dry cough, wheezing, atopy and exercise-induced dyspnea) was associated to a sensitivity of 100% (Figure 3). In no case, adding spirometric parameters improved the cumulative sensitivity for the identification of presumed asthma. Moreover, when comparing the sensitivity of the different clinical parameters between the subgroup of 383 children with $FEV_1/FVC < 90\%$, but without FEV_1 reversibility and the 205 patients with reversibility criteria, we found no significant difference between the groups (Table 3).

5. Subgroup analysis based on asthma severity

The number of included patients significantly differed in each asthma severity subgroup (respectively for severe, moderate, mild persistent and intermittent asthma: 55, 581, 203, 32; all *p-values <0,005*) (Table 4). The small number of patients included in the « intermittent » group could mainly be explained by the fact they are not representative of the average patient consulting at a tertiary University Hospital, and are therefore under-represented, if compared with the general population. Sex and BMI were not statistically different between those four groups (*p-values <0,05*).

The mean improvement in FEV_1 after bronchodilation was higher when the severity was greater: the severe asthma group showed a significantly higher increase in FEV_1 than the moderate asthma group (13.2% (SD 18.2) and 8.9% (SD 10.7), respectively; *p-value*: 0.008) and the mild group (5.0% (SD 6.9), *p-value* < 0.0001). The same significant difference was also highlighted between the moderate and the mild group as well (*p-value* < 0.0001). There was no significant difference when we compared the intermittent group with any other severity group. When we assessed patients presenting an increase of at least 12% in their FEV_1, there was a significant difference (*p-value* <0.05) in sensitivity between patients suffering from mild persistent asthma (16.3% of increase in FEV_1, in 33 children) and both moderate persistent asthma (34.3%, n=199, *p-*

value < 0.0001) and severe persistent asthma (41.8%, n=23, *p-value* < 0.0001), meaning that, as persistent asthma becomes more severe, the increase in FEV_1 criterion showed a higher sensitivity. When considering the mean basal obstruction criterion, we found lower values as asthma was more severe. The mean basal FEV_1/FVC was 79.5% (SD 10.5%) in the severe asthma group, 84.1% (SD 9.7%) in the moderate group (*p-value*: 0,0009), and 87.7% (SD 8.5%) in the mild one (*p-value* < 0.0001). When we assessed the FEV_1/FVC < 90% criterion per asthma severity, there was a significant difference (*p-value* <0.005) between each subgroup, showing that when asthma is more severe, patients present increasing obstructive spirometric values (87.5%, 72.1%, 53.2%, in the mild, moderate, and severe persistent asthma subgroups, respectively).

On the other hand, the mean change in FEF_{25-75}, was statistically different only between mild and moderate persistent asthma.

Atopy had a significant impact on asthma severity: we found more atopic patients in the severe group (51 patients, 92.7%), compared with the moderate and mild groups (78.3% (*p-value*: 0.0113) and 73.4% (*p-value*: 0.0023), respectively). No significant difference between groups was found when assessing for specific respiratory allergens and food allergy.

Discussion

Through the present multicenter study, we assessed the sensitivity of the recommended spirometric criteria in real-life settings. No study strongly affirms that the 12% threshold is an adequate cut-off value, showing a good sensitivity for the diagnosis of asthma in children. Indeed, our study, this reversibility criterion showed a very low sensitivity (30.4%) for broncho-reversibility, as a diagnostic tool for asthma in pediatrics. Thus, such a criterion does not seem to be applicable to children, if compared to adults, as previously highlighted in other studies[30]. In 2016, Hopp et al. proposed a literature review to search for the evidence that the 12% threshold was appropriate to diagnose asthma in children[26]. The authors found that most studies reported that a smaller improvement in FEV_1 should be applicable in children, and then suggested an alternative interpretative strategy, which our results support. Several authors searched for a different cut-off to assess reversibility response in pediatrics. Martinez et al. proposed a 9% threshold in children aged 7-14 years[31] and, in our population, such cut-off would show a sensitivity of 41.7% (238 children out of 571 in this age group). Kang et al. suggested to look for a 7.5% increase in FEV_1 to obtain a 50.7% sensitivity, while, in their study, the increase of 12% correlated to a 28.7% sensitivity[32]. Their results were similar to ours both for the 12% cut-off, and for the 7.5% one (sensitivity of 48.1%, with 419 children out of 871). Jat et al. affirmed that spirometry is a very useful investigation tool to diagnose asthma in children, if the test is well-performed and patients received adequate training; nevertheless, they also admitted that the diagnosis should also be based on clinical symptoms and personal history, to be more reliable[21].

As for the obstruction threshold FEV_1/CVF of 90%, such value should not be used in children to assess airways obstruction, considering the unsatisfying sensitivity of this criterion in ours and in previous studies[20]. Several authors proposed to evaluate the change in FEF_{25-75} after bronchodilation test to diagnose asthma in children[23,24,33,34]. Nevertheless, in our study, such criterion showed an even lower sensitivity than FEV_1. In a study by Dufetelle et al., the authors proposed two thresholds suggestive of bronchodilator response in asthmatic children[35]. Based on

294 spirometry z-scores, their preliminary results showed that a 0.42 z-score for FEV_1 and a –0.16 z-
295 score for FEV_1/FVC could indicate bronchoreversibility even in children with normal baseline
296 spirometry. In our cohort, when considering patients presenting with these z-score values (n=279),
297 we found a sensitivity of 32.0% (data not shown). Therefore, the usefulness of these thresholds in
298 diagnosing pediatric asthma seems limited.

299 As for patients presenting with intermittent asthma, our data showed that this group of
300 patients reported results which were not consistent with those from the other groups. These patients
301 are not representative of the typical patient referring to a tertiary University Hospital. Indeed, they
302 are most likely to be seen outside the hospital, by a general practitioner or a pediatrician since they
303 do not require a specialized expertise. Further studies in this severity group might be of interest.

304 In our study, the best sensitivity single criterion for pediatric asthma, when evaluating a
305 patient for the first time, was dry cough. When adding three clinical criteria together, such as “dry
306 cough, or wheezing or atopy” or “dry cough, or wheezing or exercise-induced dyspnea”, we
307 reached a very satisfying sensitivity (> 99%), while PFTs values were not providing sufficient
308 support to increase the diagnostic sensitivity. These simple clinical features could therefore be
309 easily and practically used in everyday clinical setting, when first evaluating children for possible
310 asthma. These findings are strongly supported by other previous studies[12,32,36] and these criteria are
311 simple to assess during a medical consultation and require no specific tool. Nevertheless, we could
312 not provide information on the accuracy of clinical parameters to diagnose asthma: indeed, to use
313 clinical data as a diagnostic tool, further studies are needed to assess, in a group of asthmatic
314 children and non-asthmatic ones, both sensitivity and specificity; these evaluations will need a
315 further prospective study.

316 In our study, we considered the two populations as one cohort, since there were no
317 differences between French and Italian enrolled children, as for sex and age. On the other hand,
318 children from the two countries differed in terms of mean basal values of FEV_1/FVC (obstruction
319 criterion) and presence of atopic conditions (i.e.: atopy, allergic rhinitis, and food allergy).

Nevertheless, the sensitivity of the FEV_1 reversibility, separely analyzed in the two countries, was 31.0% in France and 30.1% in Italy, whith no statistical difference between countries (*p-value* 0.769).

The strength of our study is the great number of included patients: we present the largest pediatric cohort focusing on this subject and including both spirometric and clinical parameters. Also, our multi-centric approach, allowed us to gather a cohort with data coming from physicians with different backgrounds, and could bring us to speculate that our results could also be extended and applied to other countries and/or settings.

Our study presents some limitations. We present a retrospective cohort study, based on information found in patients' files: for such reason, we had a few missing data for 17 patients, which nevertheless represented less than 2% of our entire cohort. Also, we included asthmatic children only, and a prospective study including any patients consulting for possible asthma could help strengthen our results and provide further insights. Our study aimed at looking at the sensitivity of the reversibility criterion only, since, in clinical practice, and from previous studies[26,30-32] as well, such a criterion seemed not to allow to properly define as asthmatic many children that present the clinical feature of the disease. Having included asthmatic patients only, we didn't assess the specificity of these parameters. The trade-off between sensitivity and specificity might therefore show that the reversibility criterion is likely to be highly specific. In general, it should be underlined that formal testing (such as spirometry or other objective testing, as methacholine) should always be performed to complete the evaluation of possible asthmatic patients. We believe that children experiencing asthma symptoms and positively responding to asthma therapy, even if presenting with a negative broncho-reversibility test, should be treated to avoid undertreatment, but also frequently re-evaluatied to obtain objective results and avoid overtreatment.

Another possible limitation is the lack of information on precise race/ethnicity of patients included in our study. Even though our populations were mainly composed by Caucasian children

(>85% in both groups, data not shown), such missing aspect may limit the generalizability of our results. Finally, we did not have data assessing F_ENO in our population. However, in a study by Murray et al., the authors showed that F_ENO as an objective test to diagnose asthma in children, has a low 44% sensitivity[36]. Nevertheless, we should consider two different aspects: firstly, our data come from real-life settings, and F_ENO measurements are not routinely evaluated by pediatricians, and therefore such data are not systematically included in patients' chart; secondly, this parameter still shows a lower sensitivity if compared with those found by our study.

We believe that our results bring an important contribution to current knowledge on the management of asthma consultations in children. The results strongly suggest that spirometric reversibility values, even though essentials for pediatric asthmatic patients, have a very unsatisfying sensitivity for the diagnosis. Clinical symptoms, on the other hand, show a very high sensitivity. For such reason, general practitioners and pediatricians could suggest a diagnosis of asthma in children, without needing, at least initially, to perform PFTs, through carefully evaluating the clinical history and the symptoms, while asthmatic patients presenting with severe forms or needing a follow-up will still require a more complete assessment in specialized centers.

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467 **Figures**

468

469 **Figure 1** – Patients included in the study.

470

471 **Figure 2** – Reversibility criteria (FEV_1/FCV < 90% and increase in FEV_1 > 12%) after
472 bronchodilation test in all 871 included children. The line shows the 12% cut-off proposed by
473 GINA guidelines. All children on the left of the line would be considered as non-asthmatics
474 following current recommendations.

475

476 **Figure 3** –Best option for cumulative sensitivity of different variables to predict a diagnosis of
477 asthma in children.

Tables

Table 1 – Characteristics of the population included in the study.

	Overall	France	Italy	*p-value*
Number of patients, n (%)	871 (100%)	342 (39.3)	529 (60.7)	< 0.001
Males, n (%)	548 (62.9%)	219 (64.0)	329 (62.2)	0.5825
Age, mean (SD)	9.2 (3.3)	9.2 (3.4)	9.3 (3.2)	0.6605
BMI, mean (SD)	18.1 (3.7)	17.6 (3.3)	18.5 (3.8)	0.0003
Basal FEV_1, in liters, mean (SD)	1.9 (0.80)	1.8 (0.79)	1.9 (0.81)	0.0728
Mean Change in FEV_1 after bronchodilation, % (SD)	8.2 (10.7)	8.1 (13.1)	8.3 (8.8)	0.7876
Mean basal FEV_1/FVC, % (SD)	84.9 (9.7)	86.1 (11.3)	84.0 (8.5)	0.0019
Mean Change in FEF25-75 after bronchodilation, % (SD)	22.1 (30.0)	20.0 (38.9)	23.4 (22.3)	0.1020
Patients treated with Anti-IgE, n (%)	39 (4.5)	11 (3.2)	28 (5.3)	0.148
Patients treated with AIT, n (%)	101 (11.6)	58 (17.0)	43 (8.1)	< 0.001
Any evokative symptom, n (%)	868 (99.7)	339 (99.1)	528 (100)	0.1418
Patients presenting with dry cough, n (%)	791 (90.8)	322 (94.1)	469 (88.7)	0.0061
Patients presenting with wheezing n (%)	553 (63.5)	138 (40.3)	415 (78.5)	< 0.001
Patients presenting with exercice-induced dyspnea, n (%)	410 (47.1)	193 (56.4)	217 (41.0)	< 0.001
Patients presenting with tight chest, n (%)	149 (17.1)	40 (11.7)	109 (20.6)	< 0.001
Patients with a history of pre-school wheezing, n (%)	315 (36.2)	119 (34.8)	196 (37.1)	0.4986
Patients with symptoms improvement after treatment, n (%)	819 (94.0)	295 (86.3)	524 (99.1)	< 0.001
Patients presenting with any atopic comorbidity, n (%)	713 (81.9)	289 (84.5)	424 (80.2)	0.1036
Patients suffering from Allergic Rhinitis, n (%)	605 (69.5)	210 (61.4)	395 (74.7)	< 0.001
Patients suffering from food allergy, n (%)	108 (12.4)	28 (8.2)	80 (15.1)	0.0024
Patients suffering from atopic dermatitis, n (%)	193 (22.2)	65 (19.0)	128 (24.2)	0.0717
Atopic patients, n (%)	678 (77.8)	244 (71.4)	434 (82.0)	0.0002
Patients sensitized to house dust mites, n (%)	471 (54.1)	151 (44.2)	320 (60.5)	< 0.001
Patients sensitized to grass, n (%)	407 (46.7)	111 (32.5)	296 (56.0)	< 0.001
Patients sensitized to cypress, n (%)*	109 (12.5)	103 (30.1)	6 (1.1)	< 0.001
Patients sensitized to birch, n (%)*	135 (15.5)	37 (10.8)	98 (18.5)	0.0021
Patients sensitized to animal danders, n (%)	314 (36.1)	108 (31.6)	206 (38.9)	0.0271
Patients sensitized to molds, n (%)	175 (20.1)	54 (15.8)	121 (22.9)	0.0108

Legend – BMI: Body Mass Index; SD: Standard Deviation; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; FEF_{25-75}: mean Forced Expiratory Flow between the 25% and 75% of the FVC; AIT: Allergen Immunotherapy.

Table 2 – Sensitivity of the reversibility criteria in children proposed by GINA guidelines for FEV_1, of bronchial obstruction in children, of the reversibility criteria for FEF_{25-75}, and of the association or either the reversibility of the FEV_1 criterion or the FEF_{25-75}, in the overall population and in the subgroups based on asthma severity patient's age, and country of origin.

		Persistent severe asthma	Persistent moderate asthma	Persistent mild asthma	Intermittent asthma	< 7 years	7-11 years	> 11 years	France	Italy
Number of patients (n)	871	55	581	203	32	221	432	218	342	529
Sensitivity of reversibility criteria with FEV_1 (%)	30.4%	41.8%	34.3%	16.3%	31.3%	32.1%	32.4%	24.8%	31.0%	30.1%
Sensitivity of obstruction criteria (%)	67.5%	87.3%	72.1%	53.2%	43.8%	48.0%	26.4%	76.6%	57.0%	74.3%
Sensitivity of reversibility criteria with FEF_{25-75} (%)	21.9%	25.5%	23.8%	16.7%	15.6%	24.9%	23.8%	15.1%	20.8%	22.7%
Sensitivity of reversibility of either FEV_1 or FEF_{25-75} (%)	36.7%	50.9%	40.1%	23.2%	37.5%	43.0%	37.5%	28.9%	38.0%	35.9%

Legend: FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; FEF_{25-75}: mean Forced Expiratory Flow between the 25% and 75% of the FVC.

The *p-value* was <0.05:

- for the FEV_1 criterion: between mild asthma and any other severity group (<0.001, <0.001, and 0.04, if compared with persistent severe, persistent moderate, and intermittent asthma, respectively);
- for the obstruction criterion: between severe and any other severity group (0.02, <0.001, and <0.001, if compared with persistent moderate, persistent mild, and intermittent asthma, respectively); between moderate and any other severity group (0.02, <0.001, < 0.001, if compared with persistent severe, persistent mild, and intermittent asthma, respectively); between the <7 years group and any other group (<0.001, and <0.001, if compared with the 7-11 years and the >11 yesrs group, respectively); between France and Italy (<0.001);
- for the FEF_{25-75} criterion: between moderate and mild (0.04); between the >11 years group and any other group (0.01, and 0.01, if compared with the <7 years and the 7-11 years group, respectively);
- for either the FEV_1 criterion or the FEF_{25-75} criterion: between severe and mild (0.001); between moderate and mild (<0.001); between the >11 years group and any other group (0.02, and 0.03, if compared with the <7 years and the 7-11 years group, respectively).

Table 3 – Sensitivity of the different clinical criteria in the whole cohort of 871 children, in the subgroup of patients in which normal FEV_1/FVC, in those with $FEV_1/FVC < 90\%$ and an increase in $FEV_1 < 12\%$ after bronchodilation, and in those presenting with reversibility criteria.

	In the whole cohort (N = 871)		Patients with $FEV_1/FVC \geq 90\%$ (N = 283)		Patients with $FEV_1/FVC < 90\%$ and increase in $FEV_1 < 12\%$ after bronchodilation (N = 383)		Patients with $FEV_1/FVC < 90\%$ and increase in $FEV_1 \geq 12\%$ after bronchodilation (N = 205)	
	Number of patients (n)	Sensitivity (%)	Number of patients (n)	Sensitivity (%)	Number of patients (n)	Sensitivity (%)	Number of patients (n)	Sensitivity (%)
Dry cough	792	90.9%	250	88.3%	350	91.4%	192	93.7%
Wheezing	553	63.5%	162	57.2%	251	65.5%	140	68.3%
Exercise-induced dyspnea	410	47.1%	122	43.1%	187	48.8%	102	49.8%
Tight chest	149	17.1%	32	11.3%	73	19.1%	44	21.5%
Pre-school wheezing	315	36.2%	108	38.2%	134	35.0%	73	35.6%
Atopy	678	77.8%	202	71.4%	306	79.9%	170	82.9%
Allergic comorbidities	713	81.9%	219	77.4%	320	83.6%	174	84.9%

We found a significant difference only between the whole cohort and the subgroup of patients with normal FEV1/FVC for the tight chest (*p-value* 0.0198) and atopy (*p-value* 0.0264) criteria.

Table 4 – Characteristics of the population, per asthma severity.

Asthma severity	Persistent severe asthma	Persistent moderate asthma	Persistent mild asthma	Intermittent asthma	Between severe and moderate asthma	Between severe and mild asthma	Between severe and intermittent asthma	Between moderate and mild asthma	Between moderate and intermittent asthma	Between mild and intermittent asthma
Number of patients, n (%)	55 (6.3)	581 (66.7)	203 (23.3)	32 (3.7)						
Males, n (%)	34 (61.8)	375 (64.5)	122 (60.1)	17 (53.1)	0.6867	0.8170	0.4273	0.2577	0.1903	0.4557
Age, mean (SD)	9.6 (3.3)	9.4 (3.2)	8.6 (3.2)	10.3 (3.6)	0.6588	0.0422*	0.3588	0.0022*	0.1244	0.0065*
BMI, mean (SD)	18.6 (3.8)	18.2 (3.7)	17.9 (3.5)	17.3 (2.8)	0.4448	0.1977	0.0955	0.3136	0.1761	0.3566
Mean Change in FEV_1 after bronchodilation, % (SD)	13.2 (18.2)	8.9 (10.7)	5.0 (6.9)	7.2 (8.9)	0.0084*	< 0.0001*	0.0847	< 0.0001*	0.3782	0.1094
Mean basal FEV_1/FVC, n (SD)	79.5 (10.5)	84.1 (9.7)	87.7 (8.5)	89.4 (10.4)	0.0009*	< 0.0001*	0.0001*	< 0.0001*	0.0028*	0.3095
Mean Change in FEF_{25-75} after bronchodilation, % (SD)	23.9 (23.8)	23.1 (32.5)	19.6 (24.5)	16.2 (21.1)	0.8588	0.2465	0.1334	0.1615	0.2358	0.4585
Patients treated with Anti-IgE, n (%)	37 (67.3)	2 (0.3)	0	0	< 0.0001*	N/A	N/A	N/A	N/A	N/A
Patients treated with AIT, n (%)	5 (9.1)	64 (11.0)	28 (13.8)	4 (12.5)	0.6609	0.3544	0.6146	0.2898	0.7946	0.8429
Patients presenting with any atopic comorbidity, n (%)	47 (85.5)	493 (84.9)	149 (73.4)	24 (75.0)	0.9053	0.0634	0.2248	0.0003*	0.1354	0.8429
Patients suffering from Allergic Rhinitis, n (%)	42 (76.4)	418 (71.9)	128 (63.1)	17 (53.1)	0.4839	0.0648	0.0253*	0.0177*	0.0224*	0.2829
Patients suffering from food allergy, n (%)	6 (10.9)	75 (12.9)	23 (11.3)	4 (12.5)	0.6707	0.9301	0.8225	0.5582	0.9464	0.8470
Patients suffering from atopic dermatitis, n (%)	14 (25.5)	140 (24.1)	34 (16.8)	5 (15.6)	0.8222	0.1411	0.2846	0.0301*	0.2723	0.8738
Atopic patients, n (%)	51 (92.7)	455 (78.3)	149 (73.4)	23 (71.9)	0.0113*	0.0023*	0.0085*	0.1518	0.3922	0.8565
Patients sensitized to house dust mites, n (%)	35 (63.6)	318 (54.7)	104 (51.2)	14 (43.8)	0.2041	0.1016	0.0713	0.3890	0.2248	0.4315

Legend: BMI: Body Mass Index; SD: Standard Deviation; FEV_1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; FEF_{25-75}: mean Forced Expiratory Flow between the 25% and 75% of the FVC; N/A: not applicable; AIT: Allergen Immunotherapy; *: statistically significant difference between the groups (*p-value* < 0.05).

Figure 1 – Patients included in the study.

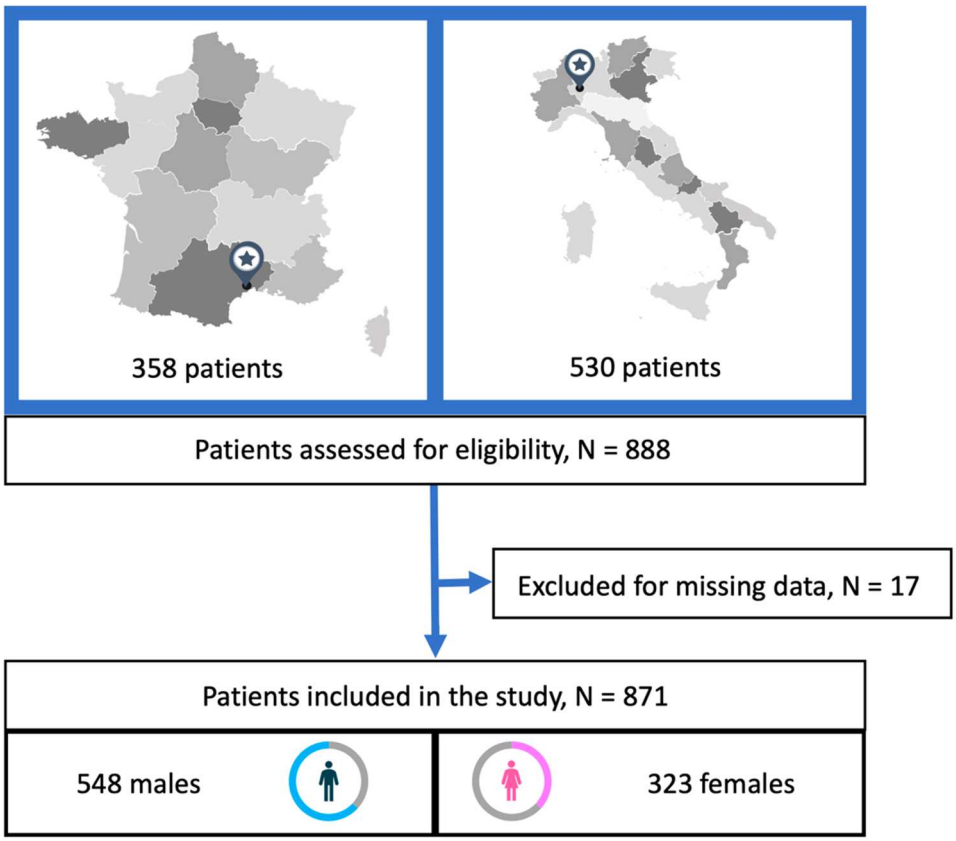


Figure 2 – Reversibility criteria ($FEV_1/FCV < 90\%$ and increase in $FEV_1 > 12\%$) after bronchodilation test in all 871 included children. The line shows the 12% cut-off proposed by GINA guidelines. All children on the left of the line would be considered as non-asthmatics following current recommendations.

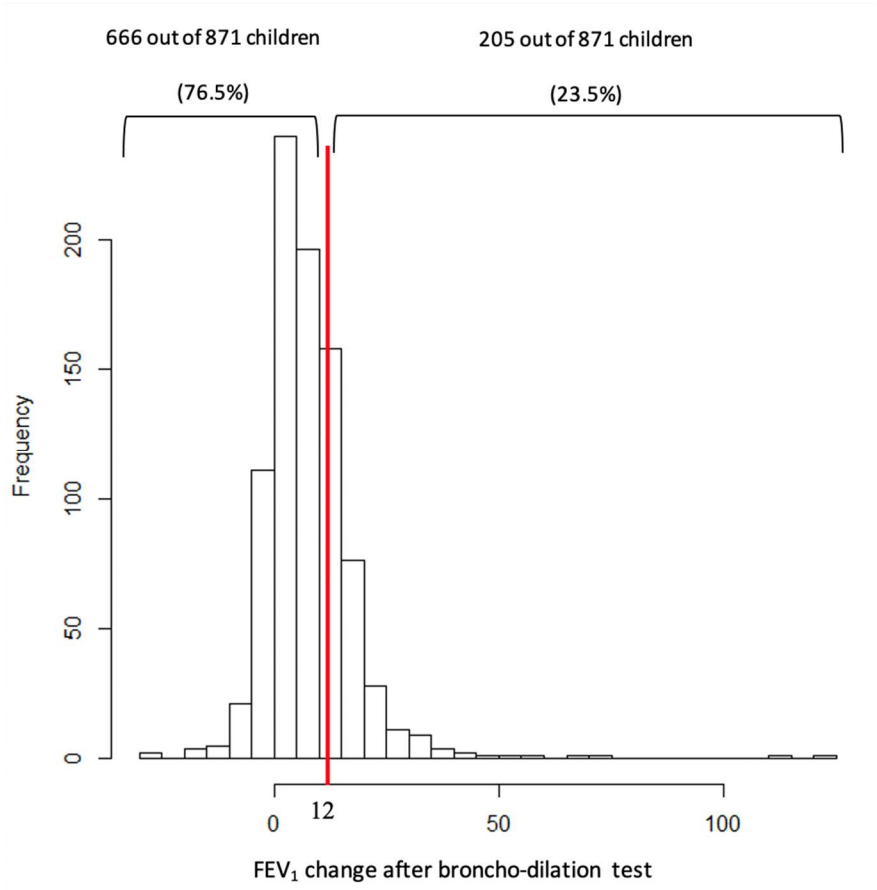
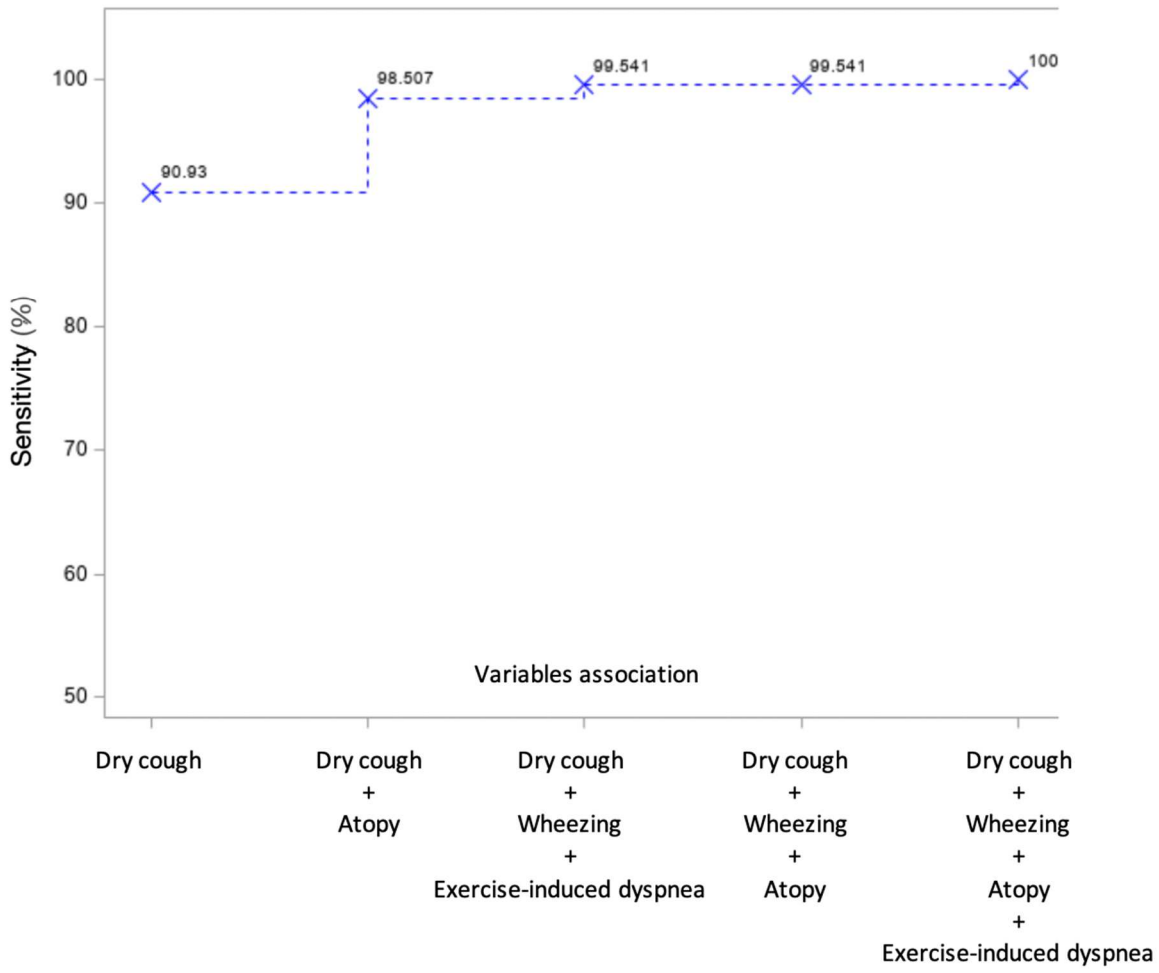


Figure 3 – Best option for cumulative sensitivity of different variables to predict a diagnosis of asthma in children.



871 children with a specialized physician diagnosis of asthma

342 children
University Hospital of Montpellier

529 children
University Hospital of Pavia

548 males

323 females

Assessment of:

Spirometric parameters

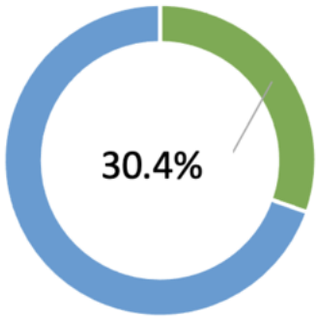
- FEV_1 reversibility criterion (+12%) – *primary outcome*
- Obstruction criterion (FEV_1/FVC < 90%)
- Small airways reversibility (FEF_{25-75} +30%)

Clinical parameters: dry cough, tight chest, wheezing, pre-school wheezing, exercise-induced dyspnea, atopy, allergic comorbidities

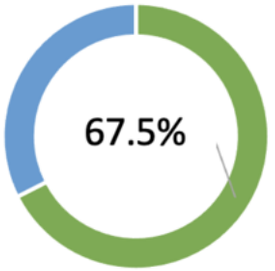
Aim: Sensitivity of spirometric and clinical parameters to identify presumed asthma in children

Sensitivity of different parameters

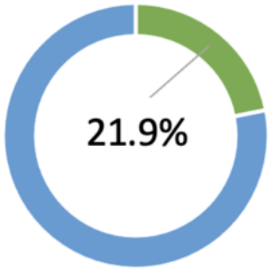
FEV_1 reversibility



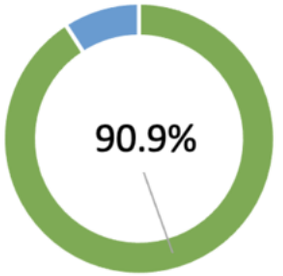
FEV_1/FVC < 90%



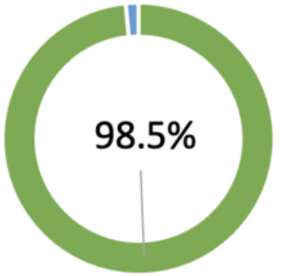
Increase of 30% of FEF_{25-75}



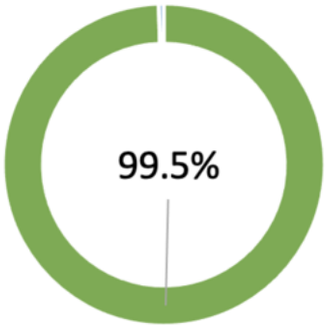
Dry cough



Dry cough or atopy



Dry cough, or wheezing or atopy



Conclusion

1. Low sensitivity of the broncho-reversibility criterion in children
2. Better sensitivity of clinical parameters