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

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1 **Sensitivity of FEV<sub>1</sub> and clinical parameters in children with a suspected asthma**  
2 **diagnosis**

3

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30

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33 **ABSTRACT (282 words)**

34 **Background:** Asthma is the most common chronic disease in children and a robust diagnosis is  
35 crucial to optimize patient care and reduce its burden. To diagnose asthma in children, GINA  
36 recommendations propose a 12% improvement in FEV<sub>1</sub> after a bronchodilation test. Nevertheless,  
37 such criterion is rarely confirmed in these patients in clinical practice.

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

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

46 **Results:** 871 children were included in the study. The reversibility criterion of 12% of FEV<sub>1</sub>  
47 showed a sensitivity of 30.4%. The three best spirometric or clinical criteria were the presence of  
48 "dry cough, or wheezing or atopy" and "dry cough, or wheezing or exercise induced dyspnea", with  
49 a sensitivity reaching 99.5%, with no added value of the spirometric parameters in the calculation of  
50 the culmulated sensitivity for the diagnosis of pediatric asthma.

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

56

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

58 **Keywords:** asthma; children; Pulmonary Function Tests; FEV<sub>1</sub>; clinical symptoms; GINA;  
59 sensitivity.  
60

## 61 **Highlights box**

62 1. What is already known about this topic?

- 63 • GINA international guidelines advise to perform pulmonary function tests to  
 64 diagnose asthma, both in children and adults. Diagnostic criteria in children require a  
 65 FEV<sub>1</sub>/FVC ratio lower than 90% and an increase of 12% of their FEV<sub>1</sub> after  
 66 bronchodilation test, based on what was observed in adults.

67 2. What does this article add to our knowledge?

- 68 • In this multicenter international retrospective cohort study, we evaluated pulmonary  
 69 function tests results of children with a physician-made diagnosis of asthma, and  
 70 collected clinical data, to assess the sensitivity of the FEV<sub>1</sub> reversibility criterion.  
 71 While reversibility criteria showed a sensitivity of 30.4%, the sensitivity of the  
 72 association of three clinical parameters was 99.5%.

73 3. How does this study impact current management guidelines?

- 74 • The results of the present work bring an important contribution to current knowledge  
 75 on asthma diagnosis in children, showing that spirometric values have a very  
 76 unsatisfying low sensitivity, especially if compared with clinical symptoms.

77

## 78 **Abbreviations**

79 AIT – Allergen Immunotherapy

80 FEF<sub>25-75</sub> – Forced expiratory flow at 25-75% of the pulmonary volume

81 F<sub>E</sub>NO – Fractional exhaled nitric oxide

82 FEV<sub>1</sub> – Forced Expiratory Volume in 1 second

83 FVC – Forced vital capacity

84 GINA – Global Initiative for Asthma

85 PFTs – Pulmonary Function Tests

86 SD – Standard Deviation

87 Se – Sensitivity

## 88 **Introduction**

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

114 the accuracy of these criteria is debated in children and other possible diagnostic methods have been  
115 investigated<sup>25,26</sup>. 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<sup>27,28</sup>.

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<sub>1</sub>),  
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.

## 123 **Methods**

### 124 *1. Study Design and included population*

125 We conducted a multicenter retrospective cohort study that included data from January 2008  
126 to January 2019. Data were collected at the Pediatric and at the Allergy Unit of the University  
127 Hospital of Montpellier, France, and at the Immunology and Allergy Pediatric Unit of the  
128 University Hospital of Pavia, Italy. The study was approved by a local ethical committee, in  
129 Montpellier (2019\_IRB-MTP\_01-06) and validated by the Ethical Committee of the University  
130 Hospital of Pavia. The study was registered on ClinicalTrials.gov (ID: NCT03814018).

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

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



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

156

## 157 2. *Outcomes of the study*

158 The primary outcome of this study was to assess the sensitivity of the reversibility criterion  
159 proposed by GINA guidelines of an increase of 12% of FEV<sub>1</sub> after bronchodilation test, compared  
160 to clinical symptoms that respond to therapy to diagnose presumed pediatric asthma.

161 The secondary endpoints were: (i) to assess the sensitivity of other spirometric parameters –  
162 such as the presence of obstructive syndrome in children, as proposed by GINA guidelines  
163 (FEV<sub>1</sub>/FVC < 90%), and the reversibility of small airways (FEF<sub>25-75</sub>), defined as an increase greater  
164 than 30% after bronchodilation test from basal values; and (ii) to evaluate, in a subgroups analysis,  
165 possible correlations between asthma severity and comorbidities.

166

## 167 3. *Statistical analysis*

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

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

## 176 **Results**

### 177 *1. Included population*

178 We included a total of 888 children with a diagnosis of asthma reached between January  
179 2008 and January 2019. 17 of them were excluded from the analysis because of missing data  
180 (Figure 1). 342 patients were included from the Montpellier University Hospital: 219 of them  
181 (64.0%) were males; their mean age at diagnosis was 9.2 years (SD 3.4). 529 patients were included  
182 from the Pavia University Hospital: 329 of them (62.2%) were males; their mean age at diagnosis  
183 was 9.3 years (SD 3.2). The two populations were not statistically different, when considering their  
184 sex and their age (*p-value*: 0.5825 and 0.6605, respectively). Moreover, basal FEV<sub>1</sub> values did not  
185 differ between the French and Italian population (1800 mL and 1900 mL, respectively; *p-value*:  
186 0.0728). For all the above reasons, statistical analysis was performed considering the two groups as  
187 a single cohort. On the other hand, since there was a significant difference between mean basal  
188 values of FEV<sub>1</sub>/FVC in the two populations and the presence of atopy, allergic rhinitis, and food  
189 allergy, we also assessed the sensitivity of spirometric criteria in the two countries, separately (*vide*  
190 *infra*).

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

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

198

### 199 *2. Primary outcome*

200 The reversibility criterion of an increase of at least 12% of the FEV<sub>1</sub> after bronchodilation  
201 test was confirmed in 266 out of 871 children (Figure 2), with a sensitivity (Se) of 30.4% (Table 2).

202 When considering children with a  $FEV_1/FVC < 90\%$ , the reversibility criterion showed a 23.5%  
203 sensitivity, being recorded in 205 children only. There was no significant difference between the  
204 two centers (31.0% and 30.1% sensitivity in the French and Italian population, respectively).  
205 Moreover, the mean change in  $FEV_1$  after bronchodilation was similar in the two centers as well  
206 (8.1% with 13.1% of SD, and 8.3% with 8.8% of SD, respectively; *p-value*: 0.79).

207

### 208 3. *Obstruction criterion and small airways criterion*

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

212 The increase of more than 30% in  $FEF_{25-75}$  after bronchodilation test was only found in 198  
213 children in our cohort (Se 21.9%), with a mean value of 22.1% (SD 30.0%) (Table 2). Furthermore,  
214 older children (>11 years group) were also less likely to achieve this reversibility criterion,  
215 compared with patients with less than 7 years of age, or between 7 and 11 years (15.1%, 24.9%, and  
216 23.8%, respectively).

217

### 218 4. *Most sensitive criteria to identify presumed asthma*

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

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

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

235

### 236 5. Subgroup analysis based on asthma severity

237 The number of included patients significantly differed in each asthma severity subgroup  
238 (respectively for severe, moderate, mild persistent and intermittent asthma: 55, 581, 203, 32; all *p*-  
239 values  $< 0,005$ ) (Table 4). The small number of patients included in the « intermittent » group could  
240 mainly be explained by the fact they are not representative of the average patient consulting at a  
241 tertiary University Hospital, and are therefore under-represented, if compared with the general  
242 population. Sex and BMI were not statistically different between those four groups (*p*-values  
243  $< 0,05$ ).

244 The mean improvement in  $FEV_1$  after bronchodilation was higher when the severity was  
245 greater: the severe asthma group showed a significantly higher increase in  $FEV_1$  than the moderate  
246 asthma group (13.2% (SD 18.2) and 8.9% (SD 10.7), respectively; *p*-value: 0.008) and the mild  
247 group (5.0% (SD 6.9), *p*-value  $< 0.0001$ ). The same significant difference was also highlighted  
248 between the moderate and the mild group as well (*p*-value  $< 0.0001$ ). There was no significant  
249 difference when we compared the intermittent group with any other severity group. When we  
250 assessed patients presenting an increase of at least 12% in their  $FEV_1$ , there was a significant  
251 difference (*p*-value  $< 0.05$ ) in sensitivity between patients suffering from mild persistent asthma  
252 (16.3% of increase in  $FEV_1$ , in 33 children) and both moderate persistent asthma (34.3%,  $n=199$ , *p*-

253 *value* < 0.0001) and severe persistent asthma (41.8%, n=23, *p-value* < 0.0001), meaning that, as  
254 persistent asthma becomes more severe, the increase in FEV<sub>1</sub> criterion showed a higher sensitivity.  
255 When considering the mean basal obstruction criterion, we found lower values as asthma was more  
256 severe. The mean basal FEV<sub>1</sub>/FVC was 79.5% (SD 10.5%) in the severe asthma group, 84.1% (SD  
257 9.7%) in the moderate group (*p-value*: 0,0009), and 87.7% (SD 8.5%) in the mild one (*p-value* <  
258 0.0001). When we assessed the FEV<sub>1</sub>/FVC < 90% criterion per asthma severity, there was a  
259 significant difference (*p-value* <0.005) between each subgroup, showing that when asthma is more  
260 severe, patients present increasing obstructive spirometric values (87.5%, 72.1%, 53.2%, in the  
261 mild, moderate, and severe persistent asthma subgroups, respectively).  
262 On the other hand, the mean change in FEF<sub>25-75</sub>, was statistically different only between mild and  
263 moderate persistent asthma.

264 Atopy had a significant impact on asthma severity: we found more atopic patients in the  
265 severe group (51 patients, 92.7%), compared with the moderate and mild groups (78.3% (*p-value*:  
266 0.0113) and 73.4% (*p-value*: 0.0023), respectively). No significant difference between groups was  
267 found when assessing for specific respiratory allergens and food allergy.

## 268 Discussion

269 Through the present multicenter study, we assessed the sensitivity of the recommended  
270 spirometric criteria in real-life settings. No study strongly affirms that the 12% threshold is an  
271 adequate cut-off value, showing a good sensitivity for the diagnosis of asthma in children. Indeed,  
272 our study, this reversibility criterion showed a very low sensitivity (30.4%) for broncho-  
273 reversibility, as a diagnostic tool for asthma in pediatrics. Thus, such a criterion does not seem to be  
274 applicable to children, if compared to adults, as previously highlighted in other studies<sup>30</sup>. In 2016,  
275 Hopp et al. proposed a literature review to search for the evidence that the 12% threshold was  
276 appropriate to diagnose asthma in children<sup>26</sup>. The authors found that most studies reported that a  
277 smaller improvement in FEV<sub>1</sub> should be applicable in children, and then suggested an alternative  
278 interpretative strategy, which our results support. Several authors searched for a different cut-off to  
279 assess reversibility response in pediatrics. Martinez et al. proposed a 9% threshold in children aged  
280 7-14 years<sup>31</sup> and, in our population, such cut-off would show a sensitivity of 41.7% (238 children  
281 out of 571 in this age group). Kang et al. suggested to look for a 7.5% increase in FEV<sub>1</sub> to obtain a  
282 50.7% sensitivity, while, in their study, the increase of 12% correlated to a 28.7% sensitivity<sup>32</sup>.  
283 Their results were similar to ours both for the 12% cut-off, and for the 7.5% one (sensitivity of  
284 48.1%, with 419 children out of 871). Jat et al. affirmed that spirometry is a very useful  
285 investigation tool to diagnose asthma in children, if the test is well-performed and patients received  
286 adequate training; nevertheless, they also admitted that the diagnosis should also be based on  
287 clinical symptoms and personal history, to be more reliable<sup>21</sup>.

288 As for the obstruction threshold FEV<sub>1</sub>/CVF of 90%, such value should not be used in  
289 children to assess airways obstruction, considering the unsatisfying sensitivity of this criterion in  
290 ours and in previous studies<sup>20</sup>. Several authors proposed to evaluate the change in FEF<sub>25-75</sub> after  
291 bronchodilation test to diagnose asthma in children<sup>23,24,33,34</sup>. Nevertheless, in our study, such  
292 criterion showed an even lower sensitivity than FEV<sub>1</sub>. In a study by Dufetelle et al., the authors  
293 proposed two thresholds suggestive of bronchodilator response in asthmatic children<sup>35</sup>. Based on

294 spirometry z-scores, their preliminary results showed that a 0.42 z-score for FEV<sub>1</sub> and a -0.16 z-  
295 score for FEV<sub>1</sub>/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<sup>12,32,36</sup> 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<sub>1</sub>/FVC (obstruction  
319 criterion) and presence of atopic conditions (i.e.: atopy, allergic rhinitis, and food allergy).



320 Nevertheless, the sensitivity of the FEV<sub>1</sub> reversibility, separately analyzed in the two countries, was  
321 31.0% in France and 30.1% in Italy, with no statistical difference between countries (*p-value*  
322 0.769).

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

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

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

346 (>85% in both groups, data not shown), such missing aspect may limit the generalizability of our  
347 results. Finally, we did not have data assessing F<sub>E</sub>NO in our population. However, in a study by  
348 Murray et al., the authors showed that F<sub>E</sub>NO as an objective test to diagnose asthma in children, has  
349 a low 44% sensitivity<sup>36</sup>. Nevertheless, we should consider two different aspects: firstly, our data  
350 come from real-life settings, and F<sub>E</sub>NO measurements are not routinely evaluated by pediatricians,  
351 and therefore such data are not systematically included in patients' chart; secondly, this parameter  
352 still shows a lower sensitivity if compared with those found by our study.

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

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- 466

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.

478 **Tables**479 **Table 1** – Characteristics of the population included in the study.

	Overall	France	Italy	<i>p-value</i>
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 <sub>1</sub> , in liters, mean (SD)	1.9 (0.80)	1.8 (0.79)	1.9 (0.81)	0.0728
Mean Change in FEV <sub>1</sub> after bronchodilation, % (SD)	8.2 (10.7)	8.1 (13.1)	8.3 (8.8)	0.7876
Mean basal FEV <sub>1</sub> /FVC, % (SD)	84.9 (9.7)	86.1 (11.3)	84.0 (8.5)	0.0019
Mean Change in FEF <sub>25-75</sub> 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 exercise-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

480 Legend – BMI: Body Mass Index; SD: Standard Deviation; FEV<sub>1</sub>: Forced Expiratory Volume in 1 second; FVC: Forced Vital  
481 Capacity; FEF<sub>25-75</sub>: mean Forced Expiratory Flow between the 25% and 75% of the FVC; AIT: Allergen Immunotherapy.

482 **Table 2** – Sensitivity of the reversibility criteria in children proposed by GINA guidelines for FEV<sub>1</sub>, of bronchial obstruction in children, of the  
 483 reversibility criteria for FEF<sub>25-75</sub>, and of the association or either the reversibility of the FEV<sub>1</sub> criterion or the FEF<sub>25-75</sub>, in the overall population and  
 484 in the subgroups based on asthma severity patient's age, and country of origin.  
 485  
 486

	871	Asthma Severity				Age Group			Country	
		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 <sub>1</sub> (%)	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 <sub>25-75</sub> (%)	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 <sub>1</sub> or FEF <sub>25-75</sub> (%)	36.7%	50.9%	40.1%	23.2%	37.5%	43.0%	37.5%	28.9%	38.0%	35.9%

487

488 **Legend:** FEV<sub>1</sub>: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; FEF<sub>25-75</sub>: mean Forced Expiratory Flow between the 25% and  
 489 75% of the FVC.

490 The *p-value* was <0.05:

- 491 - for the FEV<sub>1</sub> criterion: between mild asthma and any other severity group (<0.001, <0.001, and 0.04, if compared with persistent severe, persistent  
 492 moderate, and intermittent asthma, respectively);
- 493 - for the obstruction criterion: between severe and any other severity group (0.02, <0.001, and <0.001, if compared with persistent moderate, persistent  
 494 mild, and intermittent asthma, respectively); between moderate and any other severity group (0.02, <0.001, < 0.001, if compared with persistent severe,  
 495 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  
 496 years and the >11 yrsrs group, respectively); between France and Italy (<0.001);
- 497 - for the FEF<sub>25-75</sub> 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  
 498 years and the 7-11 years group, respectively);
- 499 - for either the FEV<sub>1</sub> criterion or the FEF<sub>25-75</sub> criterion: between severe and mild (0.001); between moderate and mild (<0.001); between the >11 years  
 500 group and any other group (0.02, and 0.03, if compared with the <7 years and the 7-11 years group, respectively).



501 **Table 3** – Sensitivity of the different clinical criteria in the whole cohort of 871 children, in the subgroup of patients in which normal  
 502 FEV<sub>1</sub>/FVC, in those with FEV<sub>1</sub>/FVC < 90% and an increase in FEV<sub>1</sub> < 12% after bronchodilation, and in those presenting with  
 503 reversibility criteria.  
 504

	In the whole cohort (N = 871)		Patients with FEV <sub>1</sub> /FVC ≥ 90% (N = 283)		Patients with FEV <sub>1</sub> /FVC < 90% and increase in FEV <sub>1</sub> < 12% after bronchodilation (N = 383)		Patients with FEV <sub>1</sub> /FVC < 90% and increase in FEV <sub>1</sub> ≥ 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	95.1%
Wheezing	553	63.5%	162	57.2%	251	65.5%	140	68.4%
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	25.2%
Pre-school wheezing	315	36.2%	108	38.2%	134	35.0%	73	33.5%
Atopy	678	77.8%	202	71.4%	306	79.9%	170	82.4%
Allergic comorbidities	713	81.9%	219	77.4%	320	83.6%	174	84.9%

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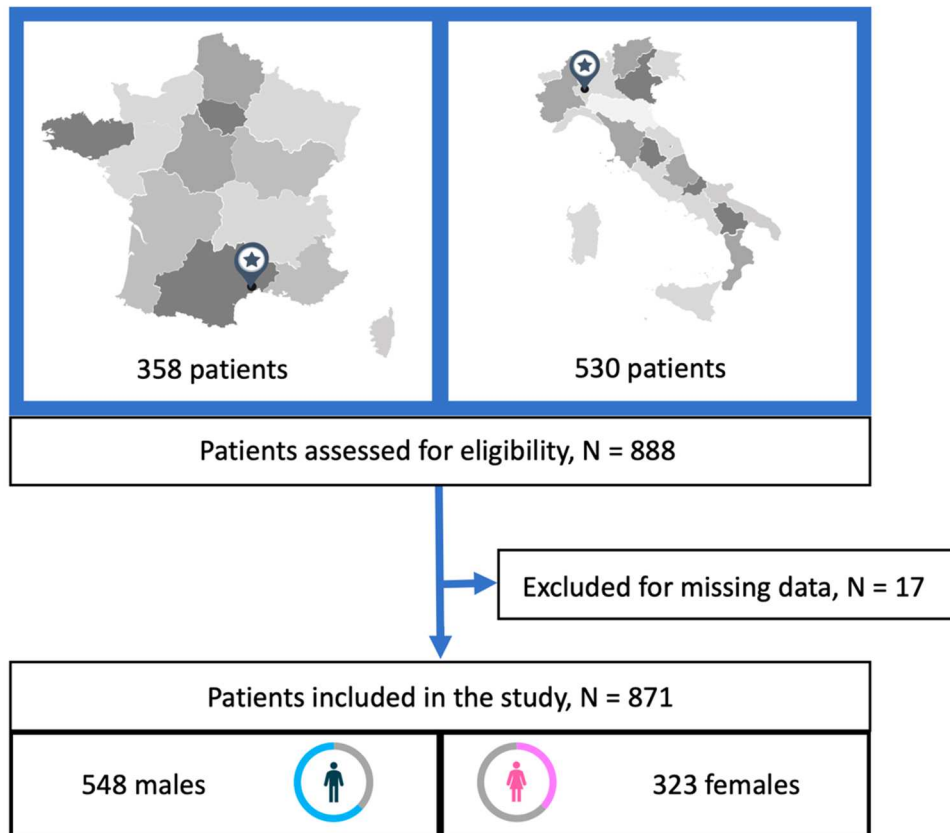
We found a significant difference only between the whole cohort and the subgroup of patients with normal FEV<sub>1</sub>/FVC for the tight chest (*p-value* 0.0198) and atopy (*p-value* 0.0264) criteria.

531 **Table 4** – Characteristics of the population, per asthma severity.  
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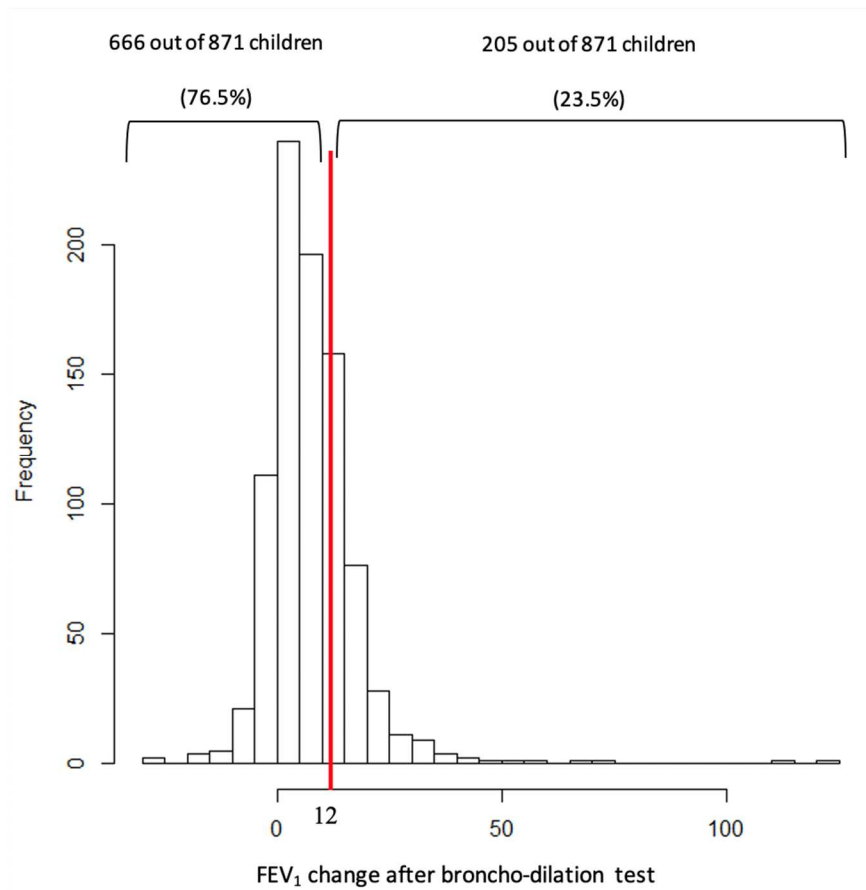
Asthma severity	Persistent severe asthma	Persistent moderate asthma	Persistent mild asthma	Intermittent asthma	Between severe and moderate asthma	Between severe and mild asthma	Between severe and intermittent asthma	Between moderate and mild asthma	Between moderate and intermittent asthma	Between mild 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 <sub>1</sub> 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 <sub>1</sub> /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 <sub>25-75</sub> 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

534 **Legend:** BMI: Body Mass Index; SD: Standard Deviation; FEV<sub>1</sub>: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; FEF<sub>25-75</sub>:  
 535 mean Forced Expiratory Flow between the 25% and 75% of the FVC; N/A: not applicable; AIT: Allergen Immunotherapy; \*: statistically  
 536 significant difference between the groups (*p-value* < 0.05).  
 537

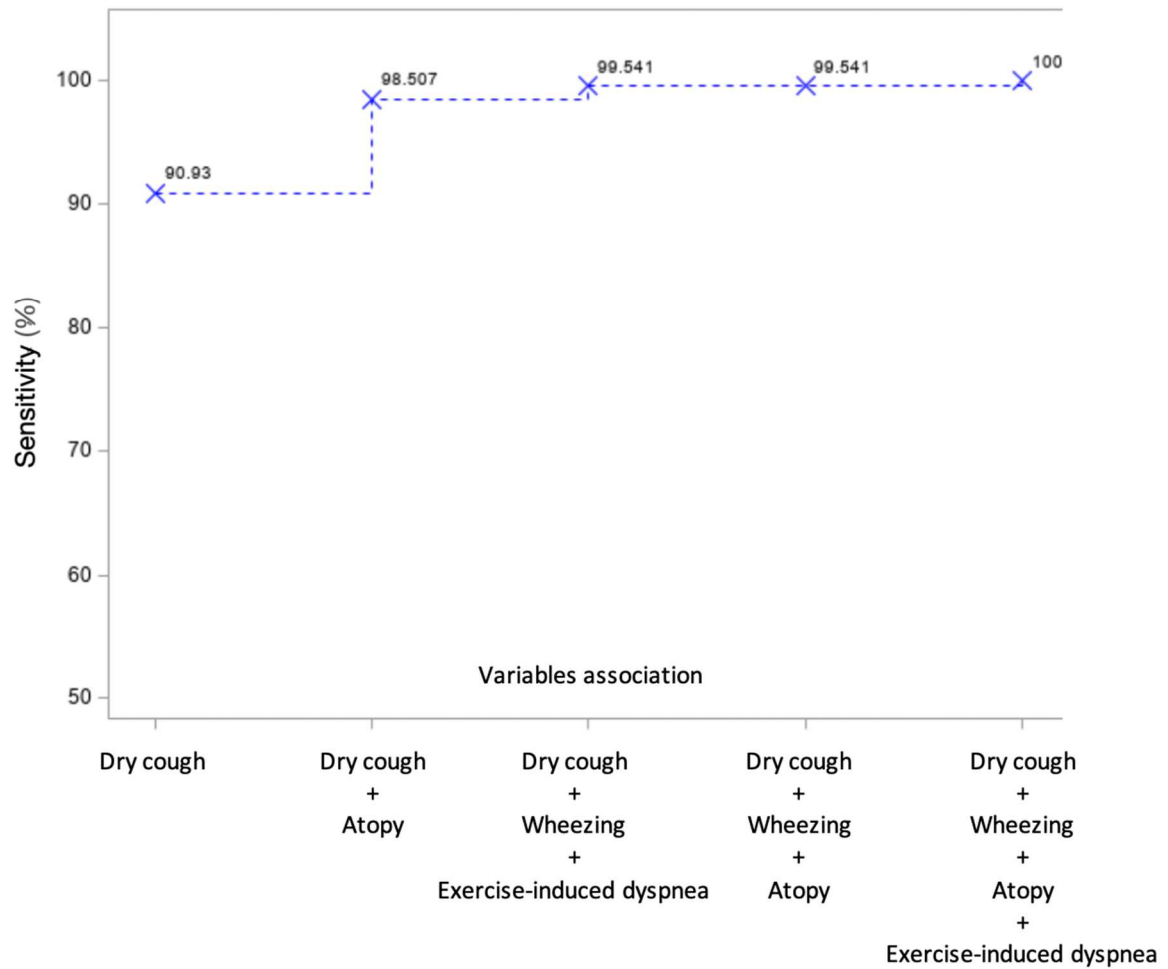
**Figure 1** – Patients included in the study.



**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

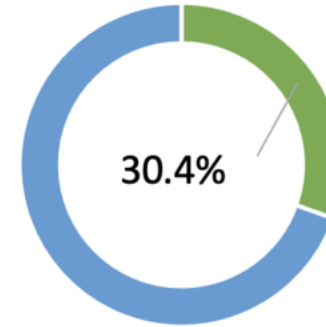
- FEV<sub>1</sub> reversibility criterion (+12%) – *primary outcome*
- Obstruction criterion (FEV<sub>1</sub>/FVC < 90%)
- Small airways reversibility (FEF<sub>25-75</sub> +30%)

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

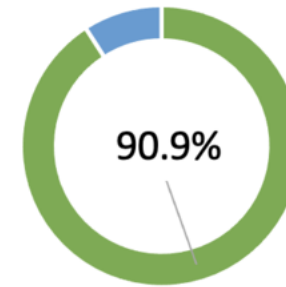
*Aim: Sensitivity of spirometric and clinical parameters to identify presumed asthma in children*

Sensitivity of different parameters

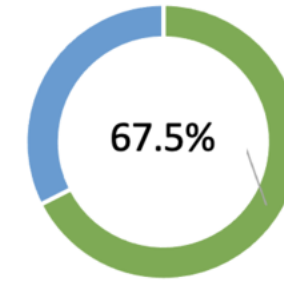
FEV<sub>1</sub> reversibility



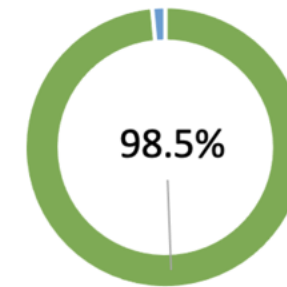
Dry cough



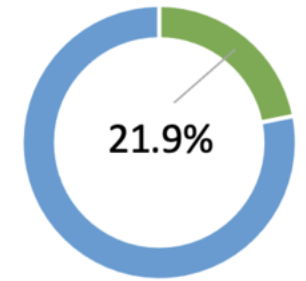
FEV<sub>1</sub>/FVC < 90%



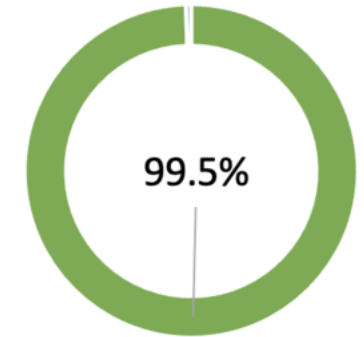
Dry cough or atopy



Increase of 30% of FEF<sub>25-75</sub>



Dry cough, or wheezing or atopy



Conclusion

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