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# Trajectory of the response to bronchodilator and respiratory outcomes in adults with asthma-like symptoms

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**Abstract**

In the real world, health professionals need to care for individuals with asthma-like symptoms who have a persistently negative bronchodilator response (BDR). Little is known about the evolution of symptoms and lung function of these individuals because they are usually excluded from studies on asthma. The aim of this study was to evaluate whether individuals with asthma-like symptoms but with a persistently negative BDR have a different evolution of symptoms and lung function compared to individuals with asthma proven by positive BDR. This prospective cohort study included adults with asthma-like symptoms. Individuals participated in two visits 12 months apart. They responded to questionnaires and underwent a spirometry test. In individuals without airway obstruction in the first visit, those with asthma-like symptoms and persistently negative BDR were less likely to lose forced expiratory volume in the first second during follow-up or progress to airway obstruction at the final visit compared to individuals with asthma proven by positive BDR. Among individuals with airway obstruction at baseline, those with asthma-like symptoms and persistently negative BDR were less likely to resolve the airway obstruction during follow-up compared to individuals with asthma proven by positive BDR. In individuals with proven asthma, the emergence or persistence of positive BDR during follow-up was accompanied by a worsening of asthma outcomes compared to the remission of positive BDR. Thus, BRD is an accessible marker of disease progression in individuals with asthma-like symptoms. In individuals with asthma proven by positive BDR, the trend in BDR was associated with the evolution of symptoms and lung function.

**Key words:** airway inflammation, bronchial hyperresponsiveness, airway remodeling, airway smooth muscle, bronchodilator response.

## Introduction

Studies indicate that the intrinsic contractility of human airway smooth muscle cells (ASM) is not different between individuals with asthma and healthy individuals [1], but inflammatory mediators produced in the airways of asthmatic individuals stimulate these cells to proliferate [2,3]. The consequences of ASM hyperplasia and hypertrophy are bronchial hyper-responsiveness (BHR), loss of lung function and irreversible airway obstruction [4].

Guidelines require evidence of BHR or bronchodilator response (BDR) for the diagnosis of asthma [5]. More than 200 ml and 12% increase of Forced Expiratory Volume in the first second ($FEV_1$) after bronchodilator in the spirometry test is evidence of BDR, but 36 to 83% of individuals with asthma have negative BDR in a single test [6-8]. Studies have shown that asthmatics with negative BDR have less eosinophilic airway inflammation [9,10]. In these individuals, the guidelines recommend repeating spirometry later to try to detect the presence of immediate BDR; or perform a bronchoprovocation test with methacholine to investigate BHR, but this last test is rarely available in clinical practice.

In the real world, health professionals need to care for individuals with asthma-like symptoms who have a persistently negative BDR on repeated spirometry. Little is known, however, about the evolution of symptoms and lung function of these individuals, because they are usually excluded from studies on asthma. Therefore, the primary objective of this study was to evaluate whether individuals with asthma-like symptoms but with a persistently negative BDR have a different evolution of symptoms and lung function compared to individuals with asthma proven by positive BDR. The secondary objective was to evaluate, in individuals with asthma proven by a positive BDR, if the evolution of BDR during follow-up is associated with the variation in the symptom score and lung function.

## Materials and Methods

We conducted this prospective cohort study in Jundiaí, a 400,000-inhabitant city in southeast Brazil. We screened consecutive individuals attending a scheduled spirometry test requested by physicians from any of the 42 public health facilities in the municipality; therefore, the sample is representative of the population of users of the public health service. The recruitment period was from January 2021 to July 2022.

We included individuals aged 18 years or older reporting typical asthma symptoms for two years or more. We excluded current smokers; smoking history above 5 pack-years; pregnant women; history of tuberculosis treatment; thoracic surgery; exposure to indoor air pollution; occupational risk factors for COPD or pneumoconiosis; and those unable to achieve American Thoracic Society (ATS) requirements in the spirometry test. All individuals included in the study

signed the informed consent. The institutional review board of the Jundiaí School of Medicine approved the study, approval number 5.221.754.

Individuals participated in two study visits twelve months apart. In each study visit, they attended a consultation with a chest physician, responded study questionnaires and underwent a spirometry test. Between study visits, individuals had one intermediate consultation with their referring physician. The researchers did not inform the referring physician about the hypothesis and purpose of the research.

***Study procedures and definitions***

In both study visits, the chest physician in charge of the research interviewed the volunteers, obtained clinical and demographic information, reviewed prescriptions and inspected medicines to record the drugs that individuals were taking during the preceding eight weeks. The record of pharmacological treatment considered the drugs and the quantity actually used. We instructed in advance that individuals bring to the study visit the prescriptions and medications so that the chest physician in charge of the research could confirm the patient's report. A trained healthcare professional applied the Asthma Control Test (ACT). This questionnaire measures the severity of asthma symptoms in a scale from five to 25, highest values indicating less symptomatology. The 19-point score discriminates controlled from uncontrolled symptoms [11]. In each study visit, individuals underwent a spirometry test with a Koko PDS® equipment and repeated the test twenty minutes after 400 mcg of salbutamol administration to measure the immediate BDR. Salbutamol was administered through a spacer. We advised individuals to discontinue bronchodilators in the 24 hours prior to carrying out the study spirometry. The spirometer was calibrated daily with a 3-liter syringe. Trained respiratory therapists executed the spirometry tests according to the ATS protocol. Briefly, all tests had at least three reproducible curves; all curves would need to have retro-extrapolated volume below 5% and end of the curve in a plateau. The researcher in charge evaluated all spirometry exams for quality. Individuals who were unable to perform spirometry according to ATS criteria were excluded from the study. The criteria for positive BDR in the spirometry test were $FEV_1$ variation after bronchodilator greater than 12% and 200 ml.

The chest physician in charge of the research identified individuals with asthma-like symptoms through an in-depth interview, physical examination and review of medical records. Some clinical evidence of asthma-like symptoms were recurrent wheezing, cough or dyspnea lasting longer than two years, lability of symptoms, symptoms improvement after ICS maintenance therapy, and symptoms relief after bronchodilator. It was crucial for the individual's inclusion in the study that there was evidence of typical asthma-like symptoms for at least 2 years.

Individuals with asthma-like symptoms and a positive BDR in at least one of the two spirometry tests performed during the study were labeled as ¨Asthma¨. Individuals with a negative BDR in both spirometry tests performed during the study were named "Asthma-like symptoms". To meet the main objective of the study, we compared the evolution of symptoms and lung function between these two groups.

Subsequently, individuals with "Asthma" were grouped according to the evolution of their BDR during follow-up in the study. Individuals with a positive BDR at the first study visit but negative BDR at the second study visit were named "Remission of BDR". Individuals with negative BDR on the first study visit who presented positive BDR on the second visit were labeled ¨Emergence of BDR¨. Individuals with positive BDR at both study visits were called ¨Persistently positive BDR¨. To meet the secondary objective of the study, we compared the evolution of symptoms and lung function between the group "Remission of BDR" and the other two groups.

We computed comorbidities whenever the individual reported current use of any pharmacological therapy for the referred illnesses [12].

***Statistical analyses***

The primary outcome was loss of lung function. Loss of more than 200 ml in $FEV_1$ between the first and last study visits defined loss of lung function because this amount of loss is large enough to ensure that it is not random according to data from two Brazilian cohorts. [13,14]. Secondary outcomes were variation in the intensity of respiratory symptoms (any improvement or worsening of the ACT score) and airway obstruction at the final study visit. Criterion of airway obstruction was $FEV_1$/FVC ratio below the lower limit of normality.

We calculated a minimum sample of 93 individuals in each group considering that 70% of individuals in the ¨Asthma¨ group would lose lung function over one year of follow-up; and 50% in the ¨Asthma like symptoms ¨ group. The basis for this estimate comes from a Brazilian cohort, which showed that 70% of adults with asthma lose lung function over one year [13]. The alfa error was set in 0.05 and the power was 80%. It is relevant that the descriptive and comparative analyses were stratified by the presence of pre-BD airway obstruction at baseline, because individuals with airway obstruction are more likely to have positive BDR [15]. We applied the Chi-Square test to compare nominal variables between two groups, while the Mann-Whitney test compared ordinal and continuous variables. We used binary logistic regression analyzes to measure the risk of loss of lung function (dependent variable) in individuals with ¨Asthma-like symptoms¨ compared to individuals with ¨Asthma¨ (independent variable). A similar model was used to assess whether the independent variable was associated with the variation of symptoms score during follow-up ($V_2$ ACT score - $V_1$ ACT score) and

airway obstruction at the last study visit (SPSS 25, IBM, Armonk, New York). We adjusted the analyzes for age, gender, lung function at baseline, symptoms score at baseline and asthma maintenance therapy at baseline because these covariates might modify the relationship between the dependent and independent variables [16-19]. In individuals with ¨Asthma¨, binary logistic regressions assessed whether the groups with ¨Persistence¨ or ¨Emergence¨ of BDR had worse asthma outcomes compared to the group with ¨Remission of BDR¨.

The method of data entry into the regression model was the Backward Likelihood Ratio. The level of significance required for a given variable to remain in the model was 0.10. We used the Hosmer-Lemeshow test (HL) to measure goodness-of-fit, and the Tolerance test (Tol) and Variance Inflation Factor (VIF) to measure collinearity. Data and model fitted together (HL > 0.05) and we observed no collinearity (Tol > 0.10 and VIF < 10).

**Results**

We screened 3,626 individuals referred for spirometry test during the recruitment period. Various respiratory and non-respiratory morbidities justified the request for spirometry by the referring physician. We did not enroll 1,891 individuals without asthma-like symptoms and 341 individuals aged bellow 18 years old. Five hundred and twelve individuals were not included because they met any exclusion criteria. Thus, we enrolled 882 individuals, but we lost the follow-up of 182. Seven hundred individuals completed all study visits, of which 437 without airway obstruction in the first study visit (110 individuals with “Asthma” and 327 with “Asthma-like symptoms”) and 263 with airway obstruction (133 individuals with “Asthma” and 130 with “Asthma-like symptoms”).

Table 1 shows baseline characteristics of individuals without airway obstruction. Individuals with ¨Asthma-like symptoms¨ had higher pre-BD lung function valuescompared to individuals with ¨Asthma¨, whilst all other characteristics were similar between groups. Table 2 shows that, among individuals with airway obstruction, those with ¨Asthma-like symptoms¨ were older, had more comorbidities, used a greater amount of asthma maintenance therapy and had a lower post-bronchodilator $FEV_1$ value at baseline compared to individuals with ¨Asthma¨.

Among individuals without airway obstruction, the dose variation of inhaled corticosteroids maintenance therapy from the first to the second study visit was similar (p 0.34) between individuals with ¨Asthma-like symptoms¨ [0 (-320, 0) mcg per day] and those with asthma proven by positive BDR [0 (-240, 200) mcg per day]. In individuals with airway obstruction, the variation in inhaled corticosteroid dose was also similar between the groups [0 (0, 400) & 0 (0, 400) mcg per day; p 0.86].

Table 3 presents the longitudinal data of individuals without airway obstruction at baseline. Compared to individuals with ¨Asthma¨, those with ¨Asthma-like symptoms¨ were less likely

to lose $FEV_1$ during follow-up or evolve to pre-BD airway obstruction at the final study visit. Table 4 describes that, among individuals with airway obstruction at baseline, those with ¨Asthma-like symptoms¨ were less likely to resolve the airway obstruction during follow-up compared to individuals with ¨Asthma¨.

In individuals with ¨Asthma¨, the emergence or persistence of positive BDR during follow-up was accompanied by worsening of asthma outcomes compared to the remission of positive BDR (Table 5).

**Discussion and Conclusions**

This study shows that, in the absence of airway obstruction at baseline, individuals with asthma-like symptoms and persistently negative BDR had more favorable outcomes compared to individuals with asthma proven by positive BDR. We are unaware of research that has investigated the disease progression of these individuals who are not usually included in studies on asthma. We did not perform a methacholine bronchoprovocation test to confirm the diagnosis of asthma, therefore, we preferred to label individuals with persistently negative BDR as ¨Asthma-like symptoms¨. It is meaningful that only individuals with typical asthma symptoms, according to the careful assessment of experienced pulmonologists, were included in the study; even so, we cannot rule out the possibility that few of them might have another illness simulating asthma. This limitation does not reduce the importance of the results and conclusions, as the intention of the study was to evaluate the disease progression of a population that frequently presents to healthcare professionals. We believe this information will help plan the management of the disease of these individuals.

In individuals with airway obstruction at baseline, those with asthma-like symptoms and persistently negative BDR had worse lung function and greater use of maintenance therapy at the initial study visit compared with individuals with asthma proven by positive BDR. During follow-up, individuals with persistently negative BDR had a lower chance of resolving their airway obstruction. We hypothesize that the persistently negative BDR in these individuals results from the control of eosinophilic inflammation due to the use of a high dose of inhaled corticosteroids, while the persistence of airway obstruction during follow-up might be due to underlying airway remodeling. This hypothesis is supported by studies that demonstrated less eosinophilic inflammation and greater concentration of biomarkers of airway remodeling in the airways of asthmatic individuals with little response to BD when compared to asthmatic individuals with an intense response to BD [9,10,15].

A cross-sectional study by Denlinger et al observed that the intensity of bronchodilator response in individuals with severe asthma was associated with self-reported exacerbations in the previous year [20]. We observed, in individuals with asthma proven by positive BDR, that

the ¨emergence¨ or ¨persistence¨ of positive BDR during follow-up was accompanied by worsening of asthma outcomes compared to the remission of positive BDR. Compared to Denlinger's study, our study has the quality of its prospective design and greater external validity, as it included individuals from all spectrums of asthma severity. Studies would need to investigate whether immediate BDR could be used as an additional information to guide the titration of asthma maintenance therapy. The methacholine bronchoprovocation test is a useful tool to guide asthma maintenance therapy in adults and children [21,22], but the lack of availability of the broncoprovocation test makes its use in clinical practice unfeasible.

It is relevant that individuals with COPD probably did not contaminate the group with airway obstruction and negative BDR because we excluded individuals exposed to risk factors for COPD and the prevalence of alpha-1-antitrypsin deficiency is usually very low [23]. Positive aspects of this study were the enrollment of individuals from various primary and secondary outpatient health facilities, the prospective design and adjusting analyzes for confounding variables. Individuals maintained regular follow-up of asthma with their referring physician between the study visits; thus, the management of asthma during the study matches real life experiences. At the baseline visit, the ¨Asthma¨ and ¨Asthma-like symptoms¨ groups differed with regard to some variables such as age, maintenance therapy and values of some spirometry test parameters. These differences, however, did not bias the conclusions because the binary logistic regressions were adjusted for covariates that could interfere with the interpretation of the results. The researchers carefully quantified maintenance therapy used by study individuals during the eight weeks preceding each of the two study visits, but they did not monitor maintenance therapy over the one year between visits. We do not foresee, however, any reason to suspect that there was a bias in the management of asthma during the follow-up, because the dozens of referring physicians who managed asthma maintenance therapy during the period between study visits were not aware of the study hypothesis. Finally, we adopted the criteria of BDR recommended in GINA, but some societies have recently proposed new guidelines for BDR [5,24].

We conclude that, in the absence of airway obstruction at baseline, individuals with asthma-like symptoms and persistently negative BDR have a more favorable evolution of lung function compared to individuals with ¨Asthma¨ proven by positive BDR. In clinical practice, this information may help plan disease management in this understudied population. In individuals with airway obstruction at baseline, the presence of asthma-like symptoms and negative BDR was associated with a lower chance of resolving the airway obstruction. Studies need to investigate whether these individuals have asthma with dominance of airway remodeling and little eosinophilic inflammation. Finally, in individuals with asthma proven by positive BDR,

the trend in immediate BDR during follow-up was associated with the evolution of symptoms and lung function.

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**Table 1. Baseline characteristics of individuals without pre-bronchodilator (BD) airway obstruction in the first study visit grouped according to the trajectory of immediate response to bronchodilator (BDR).**

| | Asthma * (N = 110) | Asthma-like Symptoms ** (N = 327) | p |
|---|---|---|---|
| Age in years – median (IQ) | 56 (44-67) | 56 (42-66) | 0.39 |
| Female gender - n (%) | 88 (80) | 265 (81) | 0.76 |
| Body mass index – median (IQ) | 31 (27-35) | 30 (26-34) | 0.14 |
| Smoking history, pack-years – median (IQ) | 0 (0-0) | 0 (0-0) | 0.65 |
| Diabetes mellitus and/or systemic arterial hypertension - n (%) | 53 (48) | 165 (51) | 0.64 |
| Depression - n (%) | 18 (16) | 49 (15) | 0.74 |
| Asthma maintenance therapy according to the GINA, n (%)<br>Step 1 or 2<br>Step 3 or 4<br>Step 5 | <br>36 (33)<br>56 (51)<br>18 (16) | <br>93 (28)<br>165 (51)<br>69 (21) | 0.47 |
| Controlled symptoms of asthma, ACT > 19 – n (%) | 48 (44) | 154 (48) | 0.45 |
| FVC % predict, pre-BD – median (IQ) | 84 (75-95) | 90 (80-101) | < 0.01 |
| FVC % predict, post BD – median (IQ) | 92 (83-103) | 91 (81-103) | 0.85 |
| $FEV_1$ % predict, pre-BD – median (IQ) | 80 (70-90) | 85 (76-99) | < 0.01 |
| $FEV_1$ % predict, post BD – median (IQ) | 88 (78-102) | 89 (78-103) | 0.59 |

* Individuals with asthma-like symptoms and positive BDR in any of the spirometry tests performed during the study. ** Individuals with asthma-like symptoms and persistently negative BDR on spirometry performed during the study.

**Table 2. Baseline characteristics of individuals with pre-bronchodilator (BD) airway obstruction in the first study visit grouped according to the trajectory of immediate response to bronchodilator (BDR).**

| | Asthma * (N =133) | Asthma-like Symptoms ** (N = 130) | p |
|---|---|---|---|
| Age in years – median (IQ) | 53 (40-63) | 59 (47-71) | < 0.01 |
| Female gender - n (%) | 95 (71) | 83 (64) | 0.19 |
| Body mass index – median (IQ) | 28 (24-34) | 28 (24-31) | 0.23 |
| Smoking history, pack-years – median (IQ) | 0 (0-0) | 0 (0-0) | 0.14 |
| Diabetes mellitus and/or systemic arterial hypertension - n (%) | 47 (35) | 66 (51) | 0.01 |
| Depression - n (%) | 21 (16) | 19 (15) | 0.79 |
| Asthma maintenance therapy according to the GINA, n (%)<br>Step 1 or 2<br>Step 3 or 4<br>Step 5 | <br>34 (26)<br>64 (48)<br>35 (26) | <br>19 (15)<br>51 (39)<br>60 (46) | < 0.01 |
| Controlled symptoms of asthma – n (%) | 52 (40) | 58 (46) | 0.38 |
| FVC % predict, pre-BD – median (IQ) | 81 (68-96) | 86 (71-100) | 0.12 |
| FVC % predict, post BD – median (IQ) | 91 (80-103) | 89 (74-102) | 0.10 |
| $FEV_1$ % predict, pre-BD – median (IQ) | 59 (46-74) | 63 (51-77) | 0.30 |
| $FEV_1$ % predict, post BD – median (IQ) | 73 (58-86) | 66 (53-81) | 0.03 |

* Individuals with asthma-like symptoms and positive BDR in any of the spirometry tests performed during the study. ** Individuals with asthma-like symptoms and persistently negative BDR on spirometry performed during the study.

**Table 3. Binary logistic regression analyzes to evaluate whether the trajectory of immediate response to bronchodilator (BDR) is associated with respiratory outcomes during the follow-up, in individuals without pre-bronchodilator (BD) airway obstruction at baseline.**

| | Odds Ratio (95 Confidence Interval) | | | |
|---|---|---|---|---|
| | Crude | p | Adjusted | p |
| Worsening of ACT score * | | | | |
| Asthma [a] | - | | - | |
| Asthma-like symptoms [b] | 0.80 (0.46-1.41) | 0.45 | 0.78 (0.44-1.38) | 0.39 |
| > 200 ml $FEV_1$ decline - pre-BD ** | | | | |
| Asthma [a] | - | | - | |
| Asthma-like symptoms [b] | 0.60 (0.39-0.93) | 0.02 | 0.41 (0.25-0.66) | < 0.01 |
| > 200 ml $FEV_1$ decline - post BD ** | | | | |
| Asthma [a] | - | | - | |
| Asthma-like symptoms [b] | 0.60 (0.39-0.93) | 0.02 | 0.52 (0.32-0.84) | < 0.01 |
| Emergence of pre-BD airway obstruction ** | | | | |
| Asthma [a] | - | | - | |
| Asthma-like symptoms [b] | 0.30 (0.16-0.57) | < 0.01 | 0.42 (0.21-0.83) | < 0.01 |
| Emergence of post-BD airway obstruction ** | | | | |
| Asthma [a] | - | | - | |
| Asthma-like symptoms [b] | 0.67 (0.22-1.99) | 0.47 | 0.81 (0.24-2.77) | 0.74 |

* Adjusted for age, gender, ACT score at baseline and asthma maintenance therapy at baseline. **Adjusted for age, gender, equivalent lung-function parameter at baseline and asthma maintenance therapy at baseline. [a] Individuals with asthma-like symptoms and positive BDR in any of the spirometry tests performed during the study. [b] Individuals with asthma-like symptoms and persistently negative BDR on spirometry performed during the study.

**Table 4. Binary logistic regression analyzes to evaluate whether the trajectory of immediate response to bronchodilator (BDR) is associated with respiratory outcomes during the follow-up, in individuals with pre-bronchodilator (BD) airway obstruction at baseline.**

| | Odds Ratio (95 Confidence Interval) | | | |
|---|---|---|---|---|
| | Crude | p | Adjusted | p |
| Worsening of ACT score * | | | | |
| Asthma [a] | - | | - | |
| Asthma-like symptoms [b] | 1.46 (0.75-2.83) | 0.26 | 1.21 (0.60-2.41) | 0.60 |
| > 200 ml $FEV_1$ decline - pre BD ** | | | | |
| Asthma [a] | - | | - | |
| Asthma-like symptoms [b] | 1.07 (0.62-1.87) | 0.80 | 1.22 (0.67-2.21) | 0.52 |
| > 200 ml $FEV_1$ decline - post BD ** | | | | |
| Asthma [a] | - | | - | |
| Asthma-like symptoms [b] | 1.16 (0.67-2.01) | 0.60 | 1.16 (0.65-2.05) | 0.62 |
| Resolution of pre-BD airway obstruction ** | | | | |
| Asthma [a] | - | | - | |
| Asthma-like symptoms [b] | 0.65 (0.35-1.22) | 0.18 | 0.52 (0.26-1.07) | 0.08 |
| Resolution of post BD airway obstruction ** | | | | |
| Asthma [a] | - | | - | |
| Asthma-like symptoms [b] | 0.44 (0.26-0.76) | < 0.01 | 0.76 (0.60-0.97) | 0.04 |

* Adjusted for age, gender, ACT score at baseline and asthma maintenance therapy at baseline. **Adjusted for age, gender, equivalent lung-function parameter at baseline and asthma maintenance therapy at baseline. [a] Individuals with asthma-like symptoms and positive BDR in any of the spirometry tests performed during the study. [b] Individuals with asthma-like symptoms and persistently negative BDR on spirometry performed during the study.

**Table 5. Binary logistic regression to assess whether the trajectory of the immediate response to the bronchodilator (BDR) is associated with the trend in symptoms and lung function in individuals with asthma proven by positive response to bronchodilator (BDR).**

| | Odds Ratio (95 Confidence Interval) | | | |
|---|---|---|---|---|
| | Crude | p | Adjusted | p |
| Worsening of ACT score * | | | | |
| Remission of BDR (n = 99) | - | | - | |
| Emergence of BDR (n = 85) | 2.21 (1.19-4.11) | 0.01 | 2.16 (1.15-4.05) | 0.01 |
| Persistently positive BDR (n = 59) | 0.93 (.44-1.96) | 0.84 | 0.,82 (0.38-1.78) | 0.61 |
| > 200 ml $FEV_1$ decline - pre-BD ** | | | | |
| Remission of BDR (n = 99) | - | | - | |
| Emergence of BDR (n = 85) | 13.07 (6.86-24.92) | < 0.01 | 14.79 (7.34-29.82) | < 0.01 |
| Persistently positive BDR (n = 59) | 2.70 (1.33-5.46) | < 0.01 | 4.48 (2.02-9.96) | < 0.01 |
| > 200 ml $FEV_1$ decline - post BD ** | | | | |
| Remission of BDR (n = 99) | - | | - | |
| Emergence of BDR (n = 85) | 0.65 (0.37-1.13) | 0.10 | 0.71 (0.39-1.27) | 0.25 |
| Persistently positive BDR (n = 59) | 0.98 (0.56-1.74) | 0.95 | 0.80 (0.44-1.47) | 0.48 |
| Pre BD airway obstruction at the last study visit ** | | | | |
| Remission of BDR (n = 99) | - | | - | |
| Emergence of BDR (n = 85) | 6.41 (3.51-11.69) | < 0.01 | 15.49 (5.87-40.86) | < 0.01 |
| Persistently positive BDR (n = 59) | 3.53 (2.10-5.94) | < 0.01 | 9.69 (4.32-21.71) | < 0.01 |
| Post BD airway obstruction at the last study visit ** | | | | |
| Remission of BDR (n = 99) | - | | - | |
| Emergence of BDR (n = 85) | 2.18 (1.25-3,80) | < 0.01 | 2.95 (1.41-6.17) | < 0.01 |
| Persistently positive BDR (n = 59) | 3.14 (1.75-5.62) | < 0.01 | 3.66 (1.70-7.88) | < 0.01 |

Comparison within three groups requires a p-value below 0.017 for statistical significance - Bonferroni correction. * Adjusted for age, gender, ACT score at baseline and asthma maintenance therapy at baseline. **Adjusted for age, gender, equivalent lung-function parameter at baseline and asthma maintenance therapy at baseline