

Bronchodilator responsiveness in wheezy infants predicts continued early childhood respiratory morbidity

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Abstract

Objective: Spirometry including bronchodilator responsiveness is considered routine in the workup of asthma in older children. However, in wheezy infants the existence of bronchodilator responsiveness and its prognostic significance remain unclear.

Methods: Infants (< 2 years) with chronic or recurrent wheezing or coughing were evaluated by infant pulmonary function testing (PFT). Maximal expiratory flow at the point of functional residual capacity ($V_{\max}$ FRC) was measured before and 20 minutes after salbutamol administration. Only infants with an obstructive profile ($V_{\max}$ FRC < 80% predicted) were included. The infants were divided into two groups with regard to whether or not a response to salbutamol was observed on PFT. A response was defined as a mean $V_{\max}$ FRC after salbutamol administration exceeding the upper confidence interval limit of individual pre-bronchodilator $V_{\max}$ FRC measurements. Follow up data was gathered after a mean of two years.

Measurements and Main Results: Sixty infants were included in the study of which 32 (53%) demonstrated responsiveness to bronchodilators. The infants in the responsive group had a significantly higher frequency of physician visits for wheezing than the non-responders (3.0 mean visits/yr vs. 1.5 respectively, $P = 0.03$), and had a higher likelihood of having received asthma medication in the last year of the follow up period (84% vs. 50% respectively, RR: 1.68[1.10–2.56]). At the end of the follow up period, more parents in the responsive group reported continued respiratory disease (71% vs. 22%, RR:3.21[1.30–7.95]).

Conclusions: Bronchodilator responsiveness can be demonstrated by infant PFT in infants with recurrent wheezing and can predict increased respiratory morbidity until 3 years of age.

Keywords

- [Respiratory function tests](#),
- [lung function tests](#),
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- [beta agonists](#)

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Introduction

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The prompt diagnosis and treatment of an infant with recurrent wheezing is a common clinical challenge(1). Although the majority of wheezy infants will outgrow their symptoms, some will be diagnosed with asthma(2). Clinical criteria, alone or in combination with laboratory or imaging studies, have proven to be insufficient in identifying children who will go on to fulfill a clinical diagnosis of asthma (3). As such, there is a lack of evidence-based recommendations for treating an infant with recurrent wheezing according to the accurate diagnosis. In addition, difficulty in early identification of asthmatic infants has limited the ability to research interventions capable of modifying the natural history of the disease.

Pulmonary function testing (PFT) is an essential part of the evaluation of asthma in both older children and adults(4). The reversal of an obstructive profile with inhaled bronchodilators (bronchodilator responsiveness, BDR) is highly suggestive of asthma(4). Persistent BDR is associated with lack of adequate control and worse clinical outcomes(5,6).

Although infants are unable to actively perform spirometry, by using rapid thoraco-abdominal compression techniques, it is possible to reproduce the flow-volume curves obtained in adults(7,8). An obstructive profile on infant PFT (iPFT) has been associated with persistent wheezing during childhood and increased airway responsiveness at age 11 years (9,10). However there remains a lack of data as to the existence of BDR in wheezy infants as well as to its prognostic significance. BDR in wheezy infants may prove to be even more useful with regard to the anticipated clinical success of bronchodilator and other asthma therapy, as well as the likelihood of developing asthma in the future.

The purpose of this study is to evaluate whether infants with recurrent wheezing or coughing and an obstructive profile on iPFT demonstrate BDR, and whether the existence of a positive response can help predict the course of the illness in early childhood.

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Study population

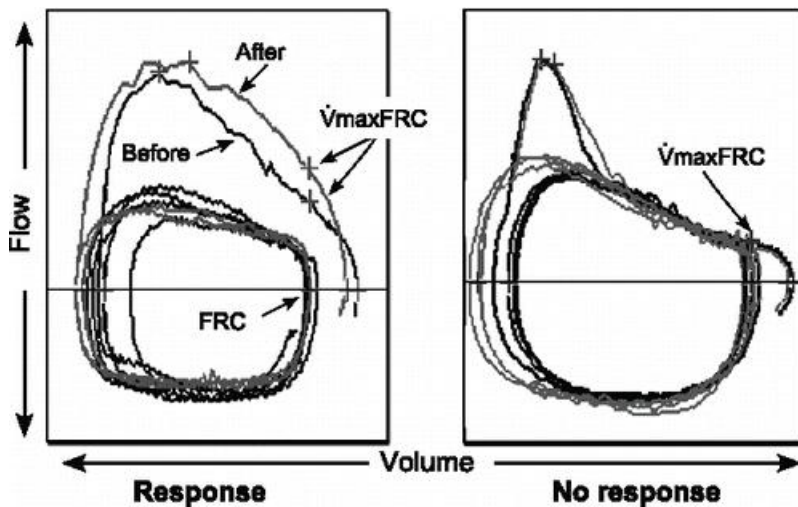
The study population consisted of infants, aged 1 to 24 months that underwent iPFT at Hadassah Medical Center between 1 Jan 2008 and 31 July 2011 due to recurrent wheezing or coughing. Infants with an obstructive profile as defined by a maximal expiratory flow at the point of functional residual capacity ($V_{max}FRC$) <80% of predicted and successful measurements before and after inhalation of salbutamol were included in the study. Preterm infants (gestational age < 36 weeks) or infants with a known chronic lung disease such as cystic fibrosis, bronchiolitis obliterans, anatomical malformations and congenital heart disease that were diagnosed before iPFT or during the follow up period, were excluded from the study.

Pulmonary function testing

iPFT was performed according to the ERS-ATS guidelines(11–13). Briefly, the infant was sedated using triclofos sodium syrup 100–150mg/kg. Flow and volume were measured using a heated pneumotachograph (Hans Rudolph, Inc. USA). Measurements of functional residual capacity (FRC_{pleth}) were done using a whole-body plethysmograph(13). The respiratory circuit was occluded at end inspiration for two to three cycles. The pressure inside the box was plotted against the pressure measured at the mouth, and the slopes of the inspiratory efforts were used to calculate the FRC. Five measurements were done to ensure reproducibility. Predicted values were calculated based on McCoy, et al(14).

The $V_{max}FRC$ was taken from the flow-volume loops measured with the tidal rapid thoraco-abdominal compression technique. Measurements were made using increasing compression pressures until a target pressure was reached at which the flow at the FRC reached a plateau (see example [Figure 1](#)). Several measurements (range: 3–7 median: 4) of $V_{max}FRC$ were made at the target pressure. The flow-volume curves were evaluated by a pediatric pulmonologist for technical artifacts (such as glottis closure or early interruption of expiration due to braking) and problematic measurements were discarded. The mean of the satisfactory $V_{max}FRC$ measurements was taken as the representative $V_{max}FRC$. Z-scores for $V_{max}FRC$ were calculated according Hoo, et al(15).

Figure 1. Examples of flow-volume loops



Measurements of $V_{\max}\text{FRC}$ were repeated in the same manner twenty minutes after an inhalation of nebulized salbutamol (0.5 mg/kg in 1.5 ml normal saline with a maximal dose of 5 mg).

Defining bronchodilator responsiveness

The main definition of BDR used in the study was a mean post bronchodilator $V_{\max}\text{FRC}$ exceeding the individualized pre-bronchodilator confidence interval. The pre-bronchodilator and post-bronchodilator $V_{\max}\text{FRC}$ measurements were log-transformed to achieve a normal distribution. For each infant, the pre-bronchodilator $V_{\max}\text{FRC}$ measurements were used to calculate individualized 95% confidence intervals. A positive bronchodilator response was defined as a mean post-bronchodilator $V_{\max}\text{FRC}$ exceeding the upper limit of the pre-bronchodilator confidence interval.

In addition, a separate analysis was performed using a traditional definition of bronchodilator responsiveness as a 20% increase in the $V_{\max}\text{FRC}$ between pre-bronchodilator and post-bronchodilator measurements. This was to allow comparison with earlier studies on the prevalence of bronchodilator responsiveness on iPFT.

Clinical data

Clinical data was gathered from the hospital and HMO electronic medical records and by structured telephone surveys (E-Appendix 1). At least three separate attempts were made to contact a parent of each participant by telephone. Chart review was conducted according to protocol (E-Appendix 2).

This study used three endpoints to assess respiratory morbidity: parent reported morbidity, use of asthma medication, and frequency of physician visits for respiratory complaints and wheezing.

Data analysis

The association between two categorical variables was assessed using the Fisher Exact Test. The comparison of a quantitative variable between two independent groups was performed using a two sample t-test for parametric variables and the Mann-Whitney U test for non-parametric variables. The comparison of a quantitative variable between repeated measurements of the same participant was performed using a paired t-test.

To assess the reliability of the bronchodilator measurements the intra-class coefficient was calculated using 3 pre-bronchodilator and 3 post-bronchodilator measurements from each infant. Statistical analysis was performed using SPSS (IBM).

The study was approved by the ethics committees of Hadassah University Hospital and the relevant HMOs. iPFT were performed, as per institutional practice, as part of the clinical evaluation of infants with persistent respiratory complaints as referred by a pediatric pulmonologist. Informed consent was obtained before the study was performed.

Results

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Infant pulmonary function testing

Of all the infants that underwent iPFT during the study time period, 60 patients met the study criteria ([Figure 2](#)). Of those, 32 (53%) demonstrated bronchodilator responsiveness (BDR). There were no significant differences between those with and without BDR in demographics or in family history of asthma or atopy ([Table 1](#)). Selected results of iPFT, including blood oxygen saturation and heart rate before and after bronchodilator, are displayed in [Table 2](#). The intra-class coefficient correlation of the VmaxFRC measurements was 0.786 [95% CI: 0.707-0.855].

Figure 2. Patient Selection Flow

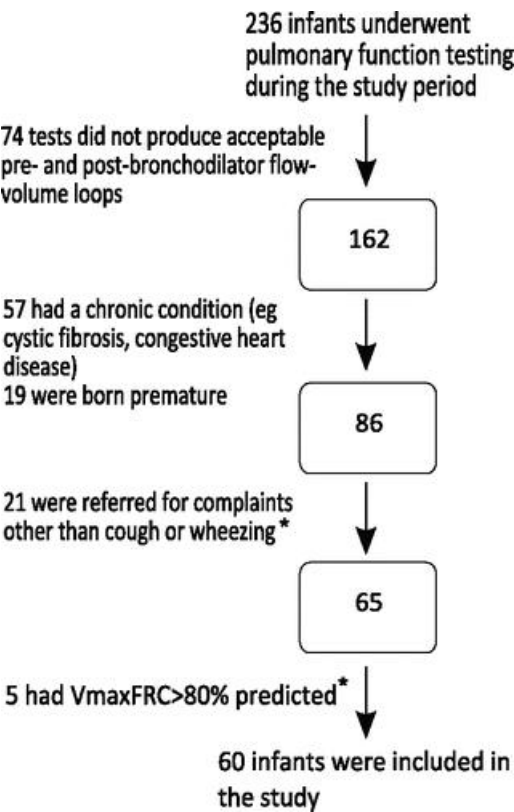


Table 1: Baseline demographic data

Table 2: Selected infant pulmonary function testing results

Follow up period

The mean follow up length was 2.3 ± 0.9 years in the non-BDR group and 1.9 ± 0.5 years in the BDR group ($p = 0.08$) with a mean age at the end of follow up of three years (range: 17 months to 5 years). HMO follow up was available for 45 (75%) infants, and telephone survey follow up was available for 38 (63%). Thirty two patients (53%) had both HMO and telephone follow up. Nine participants (15%) were lost to follow up.

The BDR group had significantly more physician visits for wheezing per year than the non-BDR group (3.0 vs. 1.5 respectively, $p = 0.039$, [Figure 3](#)). There was no difference in the number of visits for non-wheezing and non-respiratory complaints between the groups.

The relative risk of various outcomes in the BDR group as compared to the non-BDR group is displayed in [Table 3](#) and [Figure 4](#). At the end of the follow up period, a significantly higher percentage of parents in the BDR group reported that their child still suffered from respiratory symptoms (71% vs. 22%, RR-3.21 CI: 1.30–7.95).

Figure 3. Follow up visits per year by condition

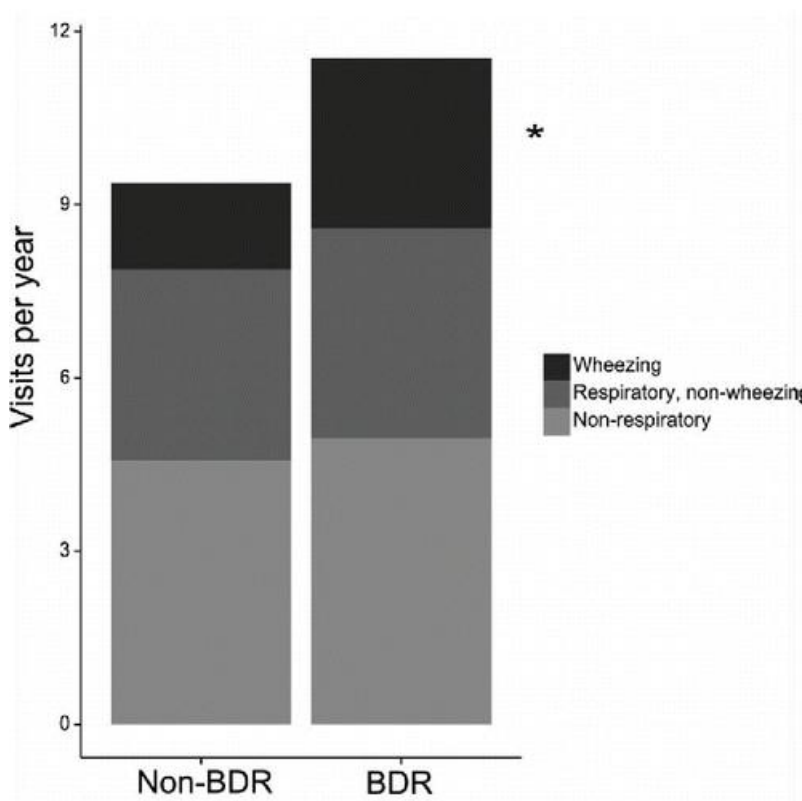
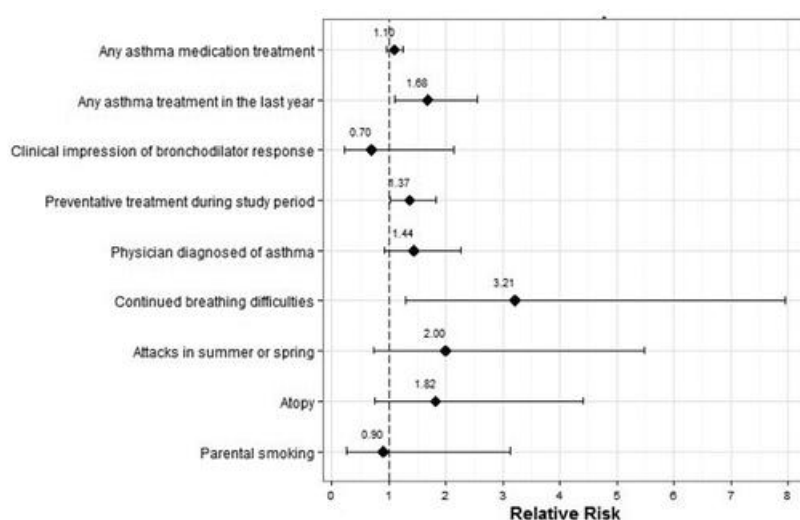


Table 3: Relative risk of various outcomes in follow up period

Figure 4. Relative risks associated with bronchodilator responsiveness



Although there was a trend for increased need for asthma medication during the study period, there was no statistically significant difference in the number of yearly prescriptions for inhaled bronchodilators, inhaled corticosteroids or oral bronchodilators between the groups (p-values: 0.19, 0.10, 0.08, respectively, E-Figure 1). In the last year of follow up, however, a significantly higher percentage of the BDR group versus the non-BDR group received some form of asthma medication (84% vs. 50%, RR = 1.68 CI: 1.10–2.56). The BDR group was also more likely than the non-BDR group to receive preventive treatment (inhaled corticosteroids for at least 1 month) at some point during the follow up period (RR-1.37 CI: 1.03–1.83).

Analysis using a traditional definition of BDR

When BDR was defined as a 20% increase in $V_{\max}$ FRC following bronchodilator 42% of the infants in the study demonstrated responsiveness. The BDR group had more follow up visits for wheezing, a higher rate of asthma medication in the last year of follow up and a higher rate of parent reported continuing respiratory morbidity (data available in E-supplement 1).

Discussion

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In a cohort of infants with obstructive iPFTs, we found that those with a measurable bronchodilator response were more likely to report ongoing symptoms. Moreover, this group was also more likely to seek physician review for wheezing and had a more persistent need for asthma medication.

BDR in infants

There is a paucity of data as to the existence of BDR in wheezy infants. Many small studies reported contradictory results with some reporting a lack of responsiveness or even a paradoxical effect^(16–21) and others showing a response^(22–25)(Table 4). The BDR rate in our study of 42% using a traditional definition and 53% using an individualized cutoff was higher than the 24% responsiveness in the multicenter study by Debley et al⁽²⁴⁾, but strengthens the observation against earlier studies that did not show bronchodilator responsiveness ^(16–18,20,26,27). The bronchodilator response rate in our study may be higher than that

found by Debley due to the fact that only infants with an obstructed profile were included as opposed to all wheezy infants in the Debley study. It is also possible that the population in our study consisted of infants with more severe respiratory morbidity that had been referred for further evaluation and in whom the rate of BDR might be higher than the Debley study.

Table 4: Earlier studies on bronchodilator responsiveness in infants

The prognostic significance of BDR

This study used three endpoints to assess respiratory morbidity: parent reported morbidity, use of asthma medications and frequency of physician visits for wheezing. In all of these endpoints the BDR group demonstrated increased respiratory morbidity as compared to the non- BDR group.

Almost all infants in the study for whom prescription data was available received some form of asthma medication during the follow up period ([Table 3](#)). The relatively high level of treatment in both groups is likely due both to the severity of respiratory morbidity in the subgroup represented by the study population (infants with particularly severe wheezing were more likely to be referred for iPFT) and also to the benign risk profile of the medications. The liberal use of medications in both groups may also explain why the BDR group did not receive more treatment on average.

The continued respiratory morbidity and the need for more medications seen in the BDR group towards the end of the follow up period might be due to a higher rate of asthmatic children in this group as compared to the non-BDR group. With the resolution of transient wheezing in the first years of life the clinical difference between the groups may have become more apparent.

One common endpoint in asthma research is physician defined asthma. In this study there was no significant difference between the BDR and non-BDR groups with regard to physician diagnoses of asthma. This data, however, should be interpreted with caution. There are no firm diagnostic criteria for asthma in this age group and use of the term varies widely among specialists and even more amongst general physicians([28,29](#)).

There was also no connection established between BDR and other factors known to be predictive of asthma such as family history of asthma or atopy. This may reflect the limitations of the data sources used in the study. We defined atopy when it was diagnosed by a physician or was reported by a parent. Other studies on the connection between atopy and asthma have required more stringent diagnostic criteria([10,28](#)). Nonetheless, another study on iPFT with more stringent criteria also failed to find a correlation between BDR and atopy or family history([24](#)).

There was also no correlation between the BDR demonstrated by iPFT and the clinical impression of BDR by the treating physician or parent as noted in the medical chart at any point following iPFT([Table 2](#)). In adults it has been shown that patients have difficulty noticing subjective improvement following bronchodilators more than placebo despite clear objective differences on PFT([30](#)). Subjective impressions of the observer may be even less reliable in infants. In this study there was no set protocol for evaluating clinical responsiveness. Clinical assessments of responsiveness by doctors, nurses and parents may be more effective if conducted in a standardized manner using objective criteria. It may be, however, that clinical assessments are fundamentally unable to differentiate asthmatics from transient wheezers. More research is required in this area.

The measurement of small airway function used in this study was VmaxFRC, the traditional measurement used in our lab, and the first to be standardized by ETS/ATS guidelines. The high intra-class coefficient seen in this study suggests reliable pre- and post- bronchodilator measurements. Some have advocated the use of raised volume techniques largely due to concerns regarding the stability of FRC during repeated

measurements. Nonetheless, studies have found good correlation between VmaxFRC and raised volume measurements both in healthy(31) infants and those with respiratory disease(32). In addition, VmaxFRC is easier to measure technically, which may have implications for more widespread clinical use. As per institutional practice, the FRC was not routinely re-measured following bronchodilator administration. It is theoretically possible that the improvement in VmaxFRC seen in the BDR group reflects a reduction in FRC independent of any effect on the small airways, although we are not aware of any such mechanism. Even if this were shown to be accurate, this study would demonstrate an improvement in respiratory mechanics following bronchodilator administration with prognostic significance. We support further studies to replicate these findings using raised volume techniques.

There is a debate as to the change in VmaxFRC that would define BDR as opposed to normal within-subject variability. Previous studies have set cut offs based on the relative increase in predicted value(31,33). In this study, individualized confidence intervals were created based on pre-bronchodilator measurements. This may be a more accurate method of defining BDR. Nevertheless, the prevalence of BDR and the findings regarding prognostic significance were similar using both the individualized and traditional definitions.

Although we have shown that BDR is able to predict continuing respiratory morbidity there might be limitations in its ability to clearly differentiate between asthmatics and transient wheezers. In this study, for example, there were some children without BDR that remained symptomatic. This may be due to limitations in test sensitivity. In older children and adults, BDR has been shown to lack sensitivity due to variations in levels of responsiveness in repeated assessments(4). In addition, a possible confounding factor is prior treatment with corticosteroids which has been shown to attenuate the levels of responsiveness in adults; this effect might be absent in children as suggested in a recent multicenter study(24,34,35). In this study, data was not systematically recorded regarding the use of corticosteroids prior to iPFT, although anecdotal evidence suggests that most subjects were not treated in the weeks prior to testing. There are also non-asthmatic causes of continued wheezing such as bronchiolitis obliterans that may not cause BDR but nonetheless continue to be symptomatic.

Conversely, there were also children in this study with BDR that did not continue to suffer from respiratory morbidity. Bronchodilator responsiveness is thought to be related to airway hyper-reactivity which is a key component of asthma(4). One study has shown there are preschool children with hyper-reactive airways, as proven by an adenosine challenge test, that do not present with symptoms of asthma five years later(36). Similarly it is possible that some infants with proven bronchodilator responsiveness will not continue to be symptomatic.

One major limitation of this study was the longitudinal follow up period of 2 years with a mean age of study participants at conclusion of less than 3.5 years. At this age, it is expected that not all forms of transient wheezing have been resolved. Diagnostic criteria for asthma at this age still lack specificity and more established tests are not yet possible. Additional studies incorporating longer follow up periods are needed.

Another limitation is that the endpoints used in the study may have been inter-related. Parents who report more respiratory morbidity may be more likely to bring their children to medical attention and the children may be more likely to receive asthma medication. Furthermore, there may have been some bias introduced by parents not being blinded to the results of iPFT. Parents of a child who was “diagnosed” with asthma may be more likely to report respiratory morbidity. However, both groups had a similar rate of non-wheezing respiratory physician visits.

Similarly, it is possible that the iPFT results influenced physicians to prescribe more asthma medication to the bronchodilator responders. Nonetheless, there are signs that the physicians in this study were not overly

influenced by the presence of BDR. They did not diagnose asthma at a higher rate in the BDR group and almost all infants in both groups continued to receive asthma medication. It is conceivable that for a physician treating a child with recurrent wheezing an obstructive profile on iPFT, even without BDR, would be sufficient to justify a working diagnosis of asthma. It is notable that only towards the end of the follow up period was there a difference in prescribing patterns. At this point any bias introduced by knowledge of the iPFT results would be expected to wane while the difference between asthmatics and transient wheezers would be expected to manifest clinically.

Another limitation of our research is the study population. The patients in our study represent a subgroup of infants that were referred by pediatric pulmonologists for iPFT as part of the clinical evaluation for recurrent wheezing. Among infants with recurrent wheezing it is likely that this population had more severe respiratory morbidity and/or a lack of a clear response to bronchodilator medication. It is possible that this subgroup does not adequately reflect all infants with recurrent wheezing.

CONCLUSIONS

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This study demonstrates that a response to bronchodilators can be demonstrated in a significant portion of infants with chronic or recurrent wheezing or coughing. In addition this study demonstrates that bronchodilator responsiveness can help predict early childhood respiratory morbidity as reported by parental surveys, need for medication, and physician diagnosis of continued wheezing. To our knowledge there have been no published longitudinal studies on the prognostic significance of BDR. If these results can be replicated in additional studies with longer longitudinal follow up, it may suggest that bronchodilator responsiveness is able to identify the wheezy infants suffering from asthma at an early stage.

In terms of the management of the wheezy infant, it still must be proven that infants with demonstrable bronchodilator responsiveness fare better under bronchodilator and/or corticosteroid therapy. It is also unclear whether anti-asthma therapy is ineffective in the majority of wheezy infants without bronchodilator responsiveness. Nevertheless this study opens important new avenues for infant asthma research.

References

1. Pedersen SE, Hurd SS, Lemanske RF, Becker A, Zar HJ, Sly PD, et al. Global strategy for the diagnosis and management of asthma in children 5 years and younger. *Pediatr Pulmonol*. Wiley Online Library; 2011;46(1):1–17. [[CrossRef](#)], [[PubMed](#)], [[Web of Science](#) ®]
2. Martinez FDF, Wright AAL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med*. 1995 Jan 19;332(3):133–8. [[CrossRef](#)], [[PubMed](#)], [[Web of Science](#) ®]
3. Savenije OEM, Kerkhof M, Koppelman GH, Postma DS. Predicting who will have asthma at school age among preschool children. *J Allergy Clin Immunol*. Elsevier Ltd; 2012 Aug;130(2):325–31. [[CrossRef](#)], [[PubMed](#)], [[Web of Science](#) ®]
4. GINA. The Global Strategy for Asthma Management and Prevention. 2015.
5. Galant SP, Morpew T, Newcomb RL, Hioe K, Guijon O, Liao O. The relationship of the bronchodilator response phenotype to poor asthma control in children with normal spirometry. *J Pediatr*. Mosby, Inc.; 2011 Jun;158(6):953–9.e1. [[CrossRef](#)], [[PubMed](#)], [[Web of Science](#) ®]

- **6.** Sharma S, Litonjua A a, Tantisira KG, Fuhlbrigge AL, Szeffler SJ, Strunk RC, et al. Clinical predictors and outcomes of consistent bronchodilator response in the childhood asthma management program. *J Allergy Clin Immunol.* Elsevier Ltd;2008 Nov;122(5):921–8.e4. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **7.** Lesnick BL, Davis SD. Infant pulmonary function testing: overview of technology and practical considerations—new current procedural terminology codes effective 2010. *Chest.* 2011 May;139(5):1197–202. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **8.** ATS/ERS statement: raised volume forced expirations in infants: guidelines for current practice. *Am J Respir Crit Care Med.* 2005 Dec 1;172(11):1463–71. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **9.** Turner SW, Palmer LJ, Rye PJ, Gibson NA, Judge PK, Cox M, et al. The relationship between infant airway function, childhood airway responsiveness, and asthma. *Am J Respir Crit Care Med.* 2004 Apr 15;169(8):921–7. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **10.** Pike KC, Rose-Zerilli MJ, Osvald EC, Inskip HM, Godfrey KM, Crozier SR, et al. The relationship between infant lung function and the risk of wheeze in the preschool years. *Pediatr Pulmonol.* Wiley Subscription Services, Inc., A Wiley Company; 2011;46(1):75–82.
- **11.** Frey U, Stocks J, Coates A, Sly P, Bates J. Specifications for equipment used for infant pulmonary function testing. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/ American Thoracic Society. *Eur Respir J.* 2000 Oct;16(4):731–40. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **12.** Sly PD, Tepper R, Henschen M, Gappa M, Stocks J. Tidal forced expirations. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/American Thoracic Society. *Eur Respir J.* 2000 Oct;16(4):741–8. [\[CrossRef\]](#), [\[PubMed\]](#)
- **13.** Stocks J, Godfrey S, Beardsmore C, Bar-Yishay E, Castile R. Plethysmographic measurements of lung volume and airway resistance. ERS/ATS Task Force on Standards for Infant Respiratory Function Testing. European Respiratory Society/ American Thoracic Society. *Eur Respir J.* 2001 Feb;17(2):302–12. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **14.** McCoy KS, Castile RG, Allen ED, Filbrun DA, Flucke RL, Bar-Yishay E. Functional residual capacity (FRC) measurements by plethysmography and helium dilution in normal infants. *Pediatr Pulmonol.* 1995 May;19(5):282–90. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **15.** Hoo A-F, Dezateux C, Hanrahan JP, Cole TJ, Tepper RS, Stocks J. Sex-specific prediction equations for Vmax(FRC) in infancy: a multicenter collaborative study. *Am J Respir Crit Care Med.* 2002 Apr 15;165(8):1084–92. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **16.** Hayden MJ, Wildhaber JH, LeSouëf PN. Bronchodilator responsiveness testing using raised volume forced expiration in recurrently wheezing infants. *Pediatr Pulmonol.* 1998 Jul;26(1):35–41. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **17.** Prendiville a, Green S, Silverman M. Paradoxical response to nebulised salbutamol in wheezy infants, assessed by partial expiratory flow-volume curves. *Thorax.* 1987 Feb 1;42(2):86–91. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **18.** Beardsmore CS, Page C, Silverman M. The response to beta-agonists in wheezy infants: three methods compared. *Respir Med.* 2004 Nov;98(11):1138–45. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **19.** Sheikh S, Castile R, Hayes J, McCoy K, Eid N. Assessing bronchodilator responsiveness in infants using partial expiratory flow-volume curves. *Pediatr Pulmonol.* 2003 Sep;36(3):196–201. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **20.** Modl M, Eber E, Weinhandl E, Gruber W, Zach MS. Assessment of bronchodilator responsiveness in infants with bronchiolitis. A comparison of the tidal and the raised volume rapid thoracoabdominal compression technique. *Am J Respir Crit Care Med.* 2000 Mar;161(3 Pt 1):763–8. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)

- **21.** Lenney W, Milner a D. At what age do bronchodilator drugs work? Arch Dis Child. 1978 Jul 1;53(7):532–5. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **22.** Tepper RS, Rosenberg D, Eigen H, Reister T. Bronchodilator responsiveness in infants with bronchiolitis. Pediatr Pulmonol. 1994 Feb;17(2):81–5. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **23.** Bar-Yishay E, Avital A, Springer C, Amirav I. Lung function response to bronchodilator nebulization via hood in wheezy infants: a pilot study. Am J Respir Crit Care Med. 2011 Jan;13(1):39–43.
- **24.** Debley J, Stanojevic S. Bronchodilator responsiveness in wheezy infants and toddlers is not associated with asthma risk factors. Pediatr Pulmonol. 2012;428(June 2011):421–8. [\[CrossRef\]](#)
- **25.** Saito J, Harris WT, Gelfond J, Noah TL, Leigh MW, Johnson R, et al. Physiologic, bronchoscopic, and bronchoalveolar lavage fluid findings in young children with recurrent wheeze and cough. Pediatr Pulmonol. 2006 Aug;41(8):709–19. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **26.** Chavasse RJ, Bastian-Lee Y, Richter H, Hilliard T, Seddon P. Inhaled salbutamol for wheezy infants: a randomised controlled trial. Arch Dis Child. 2000 May;82(5):370–5. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **27.** Hofhuis W, van der Wiel EC, Tiddens H a WM, Brinkhorst G, Holland WPJ, de Jongste JC, et al. Bronchodilation in infants with malacia or recurrent wheeze. Arch Dis Child. 2003 Mar;88(3):246–9. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **28.** Johnson C, Ownby D. Environmental epidemiology of pediatric asthma and allergy. Epidemiol Rev. 2002;24(2):154–75. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **29.** Strachan DP. The epidemiology of childhood asthma. Allergy. 1999 Jan;54 Suppl 4:7–11. [\[CrossRef\]](#), [\[PubMed\]](#)
- **30.** Wechsler ME, Kelley JM, Boyd IOE, Dutille S, Marigowda G, Kirsch I, et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. N Engl J Med. 2011 Jul 14;365(2):119–26. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **31.** Ranganathan SC, Hoo AF, Lum SY, Goetz I, Castle RA, Stocks J. Exploring the relationship between forced maximal flow at functional residual capacity and parameters of forced expiration from raised lung volume in healthy infants. Pediatr Pulmonol. 2002 Jun;33(6):419–28. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **32.** Bar-Yishay E, Springer C, Hevroni A, Godfrey S. Relation between partial and raised volume forced expiratory flows in sick infants. Pediatr Pulmonol. 2011;46:458–63. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **33.** Lagerstrand L, Ingemansson M, Bergström SE, Lidberg K, Hedlin G. Tidal Volume Forced Expiration in Asthmatic Infants: Reproducibility and Reversibility Tests. Respiration. 2002;69(5):389–96. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **34.** van Grunsven PM, van Schayck CP, Molema J, Akkermans RP, van Weel C. Effect of inhaled corticosteroids on bronchial responsiveness in patients with “corticosteroid naive” mild asthma: a meta-analysis. Thorax. 1999 Apr 1;54(4):316–22. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **35.** Hancox RJ. Interactions between corticosteroids and beta2-agonists. Clin Rev Allergy Immunol. 2006;31(2–3):231–46. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)
- **36.** Cohen S, Avital A, Hevroni A, Avenshtein A, Hadi R, Springer C. Predictive value of adenosine 5'-monophosphate challenge in preschool children for the diagnosis of asthma 5 years later. J Pediatr. Mosby, Inc.; 2012 Jul;161(1):156–9. [\[CrossRef\]](#), [\[PubMed\]](#), [\[Web of Science ®\]](#)

	BDR	Non-BDR	P-value
Subjects (% of total)	32 (53%)	28 (47%)	
Gestation (wk)	39 ± 1.6	39 ± 1.7	0.98
Birth weight (g)	3294 ± 409	3258 ± 522	0.78
Male gender	63%	68%	0.87
Family history of asthma	60%	52%	0.77
Family history of allergies/atopy	30%	42%	0.64
Age of disease onset (months)	3.5 ± 2.0	3.6 ± 2.8	0.96
Age at iPFT (months)	9.6 ± 3.5	9.9 ± 3.8	0.72
Weight at iPFT (z-score)	− 0.24	− 0.37	0.67
Length at iPFT (z-score)	− 0.52	− 0.61	0.82

All infants

	Baseline	After salbutamol	P-value
Heart rate	116 ± 15	147 ± 16	< 0.01
SpO ₂	97 ± 2	95 ± 3	< 0.01

By responsiveness

	BDR	Non-BDR	P-value
Mean FRC (% predicted)	$103 \pm 22\%$	$106 \pm 22\%$	0.59
VmaxFRC before salbutamol (z-score)	-2.04 ± 0.77	-1.73 ± 0.73	0.20
VmaxFRC after salbutamol (z-score)	-1.36 ± 0.94	-2.00 ± 0.77	< 0.01

	BDR	Non-BDR	RR	95% CI
Any asthma medication treatment during follow up period	22 (100%)	21 (91%)	1.10	0.97–1.24
Any asthma treatment in the last year of follow up	21 (84%)	13 (50%)	1.68	1.10–2.56
Clinical impression of bronchodilator response	4 (18%)	6 (26%)	0.70	0.23–2.14
Preventive treatment any time during study period	21 (95%)	16 (69%)	1.37	1.03–1.83
Physician diagnosed asthma	18 (72%)	13 (50%)	1.44	0.91–2.27
Parents reporting continued breathing difficulties	15 (71%)	4 (22%)	3.21	1.30–7.95
Attacks in the summer or spring	8 (44%)	4 (22%)	2.00	0.73–5.47
Atopy	10 (45%)	5 (25%)	1.82	0.74–4.41
Parental smoking	4 (19%)	4 (21%)	0.90	0.26–3.12

Appendix 1 – Structured Telephone Survey (translated from Hebrew)

Date _____

Participant: Father / Mother

Consent to participation: Yes / No

Full Name _____ ID number _____ Current Age _____

Pediatrician name: _____ HMO: _____

At what age did respiratory problems start? _____

Does the child still suffer from respiratory problems? Y/N

If no: At what age did they end? _____

Does the child suffer from attacks of coughing, wheezing or breathing difficulties? Y/N

If yes: With what frequency? _____

In what situations? crying / eating/ resting/ activity / other _____

Do the attacks occur during the summer (June-Aug) or spring (March-May)?

Has a physician diagnosed asthma or spastic bronchitis? Y/N

Has the child been treated in the past year with an inhalation or nebulizer? Y/N

If yes:

What treatments has he received? Ventolin (Salbutamol)/ Aerovent (Ipratropium bromide)/ Budicort (Budesonide)/

Unknown / Other _____

How many times has the child been treated in the past year? _____

For how long was the child treated each time? _____

Has the child received or has a physician suggested long term or prophylactic treatment (daily for at least 1 month)? Y/N

Has the child been hospitalized for breathing problems? _____ How many times? _____

Has the child had any sign of allergy such as: rashes / clear runny nose / food allergies/ other _____

Has anyone else in the extended family been diagnosed with asthma? Whom? _____

Had anyone else in the extended family been diagnosed with allergies? Whom?

Do either of the parents smoke? Y/N Did either smoke during the child's pregnancy?

Are there any pets in the home? Y/N

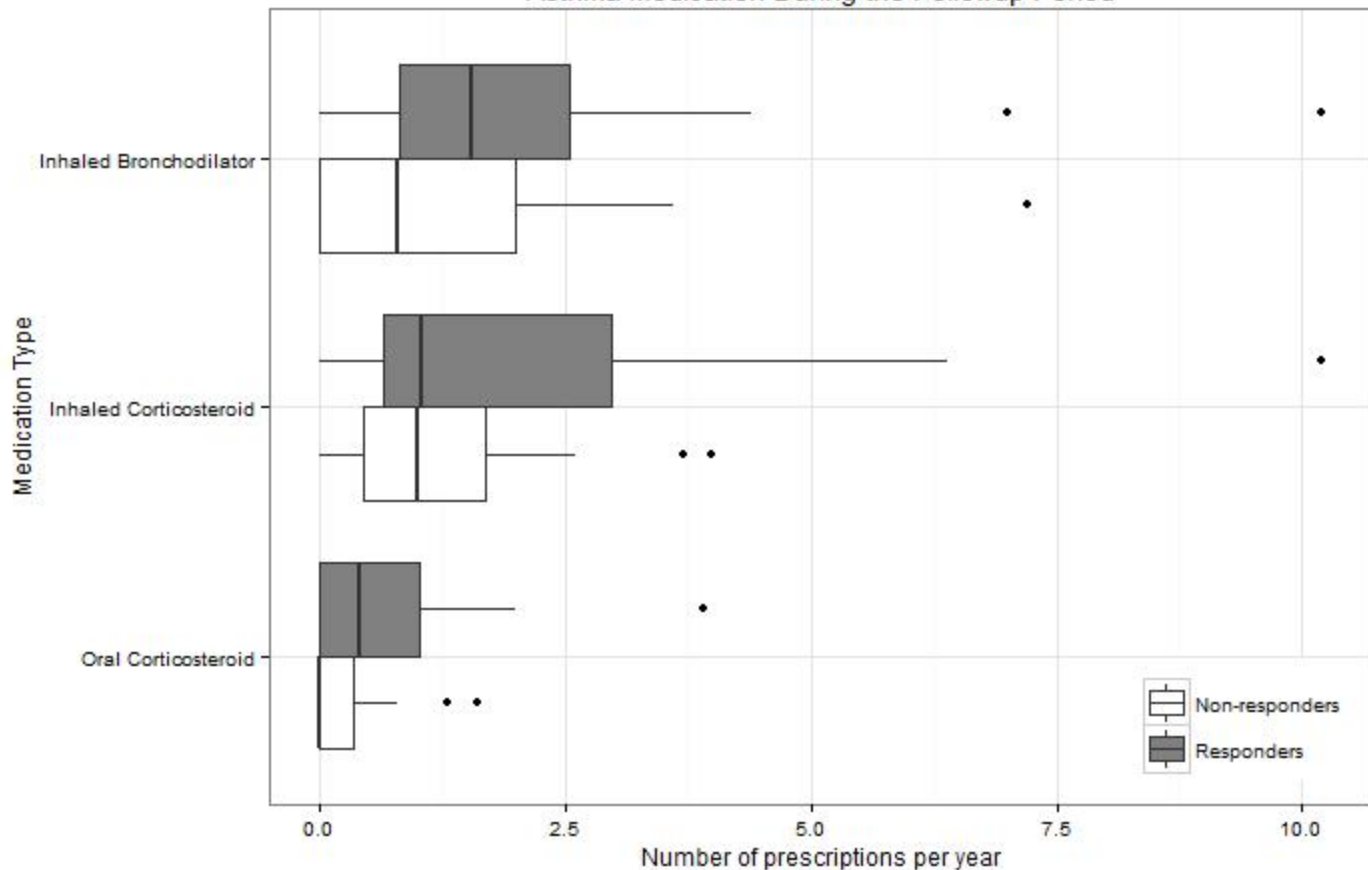
Do you have any other comments? _____

Appendix 2 Chart review protocol

Elements to be gathered:

1. Historical data (as reported to pediatrician/pulmonologist)
 - a. Family history of asthma.
 - b. Family history of allergies.
 - c. Personal history of atopy.
2. Number of physician visits during the follow up period for the following complaints. Routine or healthy follow up visits should not be included. Multiple visits for the same episode (by reviewer discretion) should only be counted once.
 - a. Wheezing – defined as either:
 - i. A visit coded as “Wheezing” or “Asthma”
 - ii. A visit due to respiratory complaints in which wheezing is noted on physical examination.
 - b. Respiratory complaints – including visits with wheezing, respiratory infections (upper and lower), coughing, or shortness of breath. Does not include isolated rhinorrhea.
 - c. Total visits.
3. Number of prescriptions for asthma medication during the follow up period. Depending on availability of data can either be prescriptions that were given by a physician or prescriptions actually purchased by the patient. Divided into:
 - a. Bronchodilators
 - b. Inhaled corticosteroids
 - c. Oral corticosteroids
 - d. Montelukast
4. Date of final prescription for asthma medication.
5. Clinical response to asthma medication as noted by treating physician or reported by parent.
6. Number of total hospitalizations and hospitalizations for respiratory complaints during the follow up period.
7. Physician diagnosed asthma – a single visit coded as “Asthma” by any physician during the follow up period is sufficient.
8. Last recorded weight and height (if available)

Asthma Medication During the Followup Period



E-Supplement-1: Analysis using 20% cutoff

In many studies bronchodilator responsiveness defined as a relative increase of 20% over pre-bronchodilator VmaxFRC. Although the analysis in the paper were reported using a more statistically rigorous definition, for the purpose of comparison with earlier studies we have presented an analysis of our data in which bronchodilator responsiveness has been defined by the traditional increase of 20%.

Baseline demographic data (cf Table 1)

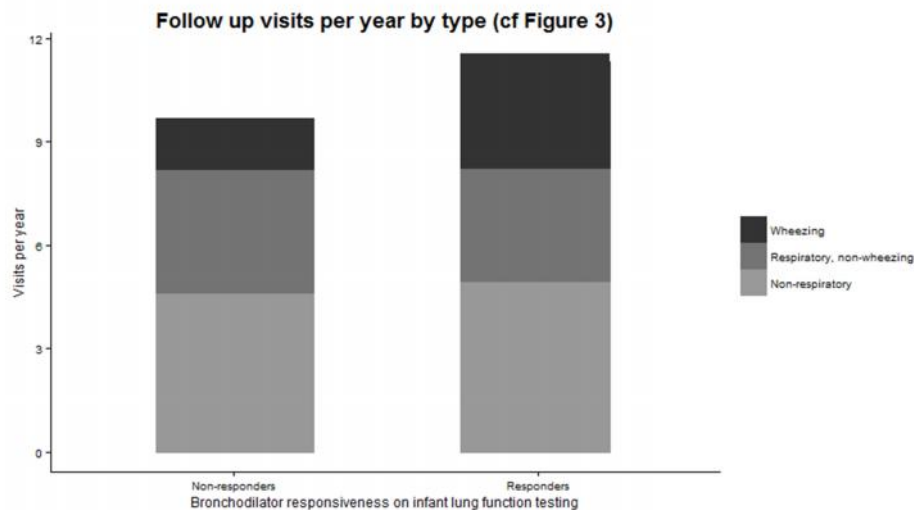
	Responders	Non-responders	P-value
Subjects (% of total)	25(42%)	35 (58%)	
Gestation (wk)	39±1.7	39±1.6	0.41
Birth weight (g)	3319±360	3247±527	0.55
Male gender	64%	66%	1
Family history of asthma	68%	48%	0.27
Family history of allergies/atopy	29%	40%	0.71
Age of disease onset (months)	3.6±2.1	3.5±2.5	0.95
Age at iPFT (months)	9.5±3.6	9.9±3.7	0.68
Weight at iPFT (z-score)	-0.37	-0.24	0.66
Length at iPFT (z-score)	-0.64	-0.52	0.71

iPFT- infant pulmonary function testing, ±SD

Twenty-five out of 60 study participants displayed bronchodilator responsiveness (42%). There was no difference in baseline demographic characteristics.

Follow up period

The BDR group had significantly more visits for wheezing per year (Figure 3, 3.4 vs. 1.5, $p=0.03$). There was no significant difference in the frequency of non-wheezing respiratory or non-respiratory visits.



During the follow up period almost all infants received some form of asthma medication at some point and there was no difference between the groups. In the last year of follow up, however, a significantly higher percentage of the BDR group received any asthma medication (84% vs. 55%, $p=0.03$).

At the end of the follow up period, a significantly higher percentage of parents in the BDR group reported that their child still suffered from respiratory problems (67% vs. 30%, $p=0.03$).

Differences in physician diagnosed asthma, exacerbations in spring/summer, and presence of atopy were not statistically significant.

Figure 4 shows the relative risks of the various outcomes in the BDR group as compared to the non-BDR group.

Relative risks associated with bronchodilator responsiveness (cf Figure 4)

