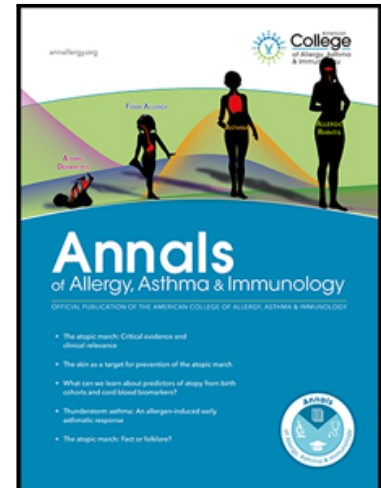


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Impulse oscillometry and free-running tests for diagnosing asthma and monitoring lung function in young children

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Author Contribution:

The study protocol and manuscript were written by the investigators (PM, AP, MM). Data were collected by the study physician (JB) and analyzed by the principal investigators (JB, PM, and MM). The study was supervised by TJ and SR. JB has primarily drafted the

manuscript but other authors have also drafted and critically reviewed the manuscript and approved the version to be published and agrees to be accountable for all aspects the work related to its accuracy and integrity. The funding agencies covered all the costs of the study but played no role in the study design, data analysis, or manuscript preparation.

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Keywords:

asthma, bronchial hyper-responsiveness (BHR), free-running test (FRT), lung function, oscillometry, inhaled corticosteroid (ICS), children's health

Abbreviations:

BHR, bronchial hyperresponsiveness; C-ACT, Childhood Asthma Control Test; EIB, exercise-induced bronchoconstriction; FeNO, exhaled nitric oxide; FRT, free running test; ICS, inhaled corticosteroid

Background: Separating viral-induced wheezers from asthmatics is challenging, and there are no guidelines for children under 6 years of age. Impulse oscillometry is feasible beginning 4-year old children.

Objective : To explore the use of impulse oscillometry in diagnosing and monitoring asthma in young children and evaluating treatment response to inhaled corticosteroid.

Methods: Forty-two children (median age 5.3 years, range 4.0–7.9 years) with doctor diagnosed asthma and lability in oscillometry were followed for 6 months after initiation of inhaled corticosteroid treatment. All children performed the 6-minute free-running test and impulse oscillometry at three time points. After the baseline, they attended a second visit when they had achieved good asthma control, and a third visit about 60 days after the second visit. A positive ICS-response was defined as having greater than 19 points in ACT and no hyperreactivity on the third visit.

Results: In total, 38/42 children responded to ICS treatment. Exercise-induced increases of resistance at 5 Hz decreased after ICS-treatment (61% vs. 18% vs. 13.5%, $p < .001$), and running distance during the 6-minute test was lengthened (800m vs. 850m vs. 850m, $p = .001$). Significant improvements in childhood asthma control (C-ACT) scores occurred between the baseline and subsequent visits (21 vs. 24 vs. 24, $p < .001$) and acute doctors' visits for respiratory symptoms [(1, (0–6) vs. 0, (0–2), $p = .001$]. Similar profiles were observed in children without aeroallergen sensitization and among those under 5 years of age.

Conclusion: Impulse oscillometry is a useful tool in diagnosing asthma and monitoring lung function in young children.

Introduction

The prevalence of childhood asthma varies in European birth cohorts, possibly at least to some extent due to lack of universal consensus guidelines on diagnosing early childhood asthma.¹ Typical symptoms are wheezing and coughing, with bronchial hyperresponsiveness (BHR).² Many young children who have wheezing episodes have no asthma symptoms at school age, making it difficult to separate virus-induced wheezers from asthmatics in early childhood.³ Clinical tools predict whether young children will go on to develop childhood asthma, but a negative result using the Asthma Predictive Index does not rule out asthma in later life.⁴ This is why clinical diagnosis is challenging in children under 6 years old.

Impulse oscillometry is a non-invasive lung function tool that only requires passive patient co-operation with normal breathing via a mouthpiece. The impulse oscillometry utilizes externally applied pressure signals and their resultant flows to determine resistance and reactance, the components of respiratory impedance. Peripheral airway obstruction typically results in negative frequency dependence of resistance. Therefore, resistance at lower frequencies (R5) is thought to reflect both peripheral and central airway resistance, whereas with increasing frequencies (R20), resistance at more central airways.⁵

Impulse oscillometry is feasible in 4-year-old children, and asthmatic children have abnormal bronchodilator responses.⁶ Preschool oscillometry has been shown to predict lung function at school age, which is why it can be useful in clinical practice for predicting persistent lung symptoms into adolescence.^{7,8} According to the European Respiratory Society recommendations, oscillometry can be performed from the age of 2 years, and the 6-minute free-running test (FRT) can be used from the age of 4 years.⁹

A Finnish study reported that, when healthy children aged 3–7 years took part in the 6-minute free-running test, the highest 95% confidence limit for maximal exercise-induced

change in respiratory resistance at 5 Hz was 32.5%.¹⁰ According to the Finnish national asthma guidelines, a change in resistance at 5 Hz of $\geq 40\%$ between baseline and the period following exercise or bronchodilation tests is a diagnostic value for exercise-induced bronchoconstriction (EIB) at 3–7 years of age, and it can be used as a major diagnostic feature of asthma together with symptoms.¹¹

A minimum level of 35 ppb of exhaled nitric oxide (FeNO) in asthmatic children predicts a good response to an inhaled steroid.¹² The full-term use of an inhaled corticosteroid (ICS) rarely relieves to chronic cough without atopy.¹³ Phenotype-based treatment has previously been described,¹⁴ and a good response to inhaled steroid treatment has been predicted for children with eosinophilia $\geq 0.30 \text{E9/l}$ and/or those sensitized to aeroallergens.^{14,15}

A number of studies have shown that ICS reduced BHR and decreased FeNO among adults and children aged 5–16 years with asthma.¹⁶⁻²³ Additionally, BHR improved among children aged 5–12 years when measured in two studies using the methacholine challenge.^{23,24} The fall of FEV1 observed during 6-minute FRT improved within 3–6 weeks when children aged 7–12 years received ICS treatment.²⁴ It has previously demonstrated that ICS decreased FeNO, asthma symptoms, and the use of rescue medication, and was tolerated well by children aged 4–7 years with wheezing due to multiple triggers.²³ Significant proportions of asthmatic children respond poorly to ICS.²⁵ Among 288 6–18-year-old asthmatic children, ICS treatment reduced exacerbations, but one-third experienced exacerbations during ICS treatment.²⁶

In this study, we evaluated the feasibility of impulse oscillometry together with clinical assessment in the evaluation of ICS treatment responses in Finnish preschool children aged 4–7 years. We hypothesized that 6-minute FRT combined with impulse oscillometry could supplement the routine clinical evaluation of preschool-age children with suspected asthma.

Methods

The study was carried out on children aged 4–7 years with mild or moderate asthma. It was conducted at two sites in Helsinki, Finland, from November 28, 2017, to May 15, 2020: the tertiary Skin and Allergy Hospital and the Mehiläinen Töölö private clinic. Apart from age, the other inclusion criteria were typical asthma symptoms, such as wheezing, cough, and/or dyspnea; the ability to cease any ICS treatment for 30 days before testing; and doctor-diagnosed asthma. The exclusion criteria included using ICS in the past 30 days, an acute respiratory infection in the past 14 days, and preterm birth. We also excluded children with a respiratory diagnosis, another chronic lung disease or a neurological or cardiovascular disease with respiratory symptoms, and active implanted equipment, such as a pacemaker.

Of the 53 children, 45 were seen at the hospital and eight were seen at the clinic. Both study sites carried out the 6-minute FRT, but there were missing data for three of the eight children who underwent this procedure at the clinic. They were excluded from this part of the analysis. We found that 48 of the 50 children who underwent 6-minute FRT had as compared to baseline, had $\geq 40\%$ increase in respiratory resistance at 5 Hz or $\geq 40\%$ decrease in resistance at 5 Hz on the bronchodilatation test. In addition to the three clinic subjects with missing data who were excluded from the analysis, a further four children dropped out of the study, and four without significant bronchodilatation improvements or exercise-induced respiratory increases were excluded. Ultimately, 42 of the 53 children were included in the final analysis. Of these, 31 (74%) were boys, and 31 (74%) had no ICS treatment in the past six months (Figure 1).

Questionnaire

Background data were collected for the case report form, including the child's sex; whether they had ever been diagnosed by a physician with atopic eczema, asthma, or allergic

rhinitis; and whether they had a history of wheezing when they did not have an infection. We also collected data on parental asthma and current smoking. The Childhood Asthma Control Test (C-ACT)²⁷ was completed during every visit.

Each acute doctor-diagnosed wheezing episode and physician visit with respiratory symptoms six months before and six months after the baseline was also recorded. These included primary care and emergency department visits and were obtained from the national Finnish registries.

Laboratory tests

Children underwent laboratory testing, if clinically indicated, and the following results were collected: blood count eosinophils, C-reactive protein, and skin-prick tests or specific immunoglobulin E tests for aeroallergens. A serum immunoglobulin E value of over 0.35 kU/l, using the Phadiatop test (Phadia AB, Uppsala, Sweden), was considered a positive reaction. Birch, timothy, mugwort, dog, cat, horse, *Cladosporium herbarum*, and *Dermatophagoides pteronyssinus* were included in the skin-prick test, and a minimum wheal size of 3 mm was considered positive.

Prerequisites for testing

Beta2 agonists were not administered for 12 hours before the tests. If the child had acute respiratory infection symptoms or fever at the baseline visit or Visit 3, only the oscillometry and bronchodilatation test were performed.

Study visits

Visit 1 provided the baseline data. The second study visit took place when the child achieved good asthma control, with a C-ACT of >19 points; this always took place at ≥ 4 weeks after the baseline visit. The median time between Visits 1 and 2 was 43.5 days (range

32–68 days). The target for days between Visits 2 and 3 was 50–70 days, and the median time between visits that was achieved was 68 days (range 57–100 days; Figure 1).

Impulse oscillometry

The baseline oscillometry test was performed according to the criteria of the European Respiratory Society and the American Thoracic Society.²⁸ We documented resistance at 5 Hz and at 20 Hz, the difference between resistance at 5 Hz and 20 Hz, and reactance at 5 Hz. Obstruction was defined as a Z-score of ≥ 1.65 SD of the prediction for resistance at 5 Hz.²⁹

The 6-minute FRT and bronchodilatation test

The 6-minute FRT³⁰ was performed during every study visit, but two of the 42 children did not perform the FRT at baseline because of a significant obstruction discovered via the oscillometry test. If the children had an acute respiratory infection during the third visit, only oscillometry, with a bronchodilatation test, was performed at that point. The heart rate target was a minimum of 170 beats per minute for 6 minutes. Impulse oscillometry was performed immediately before the test started, then at 1 and 5 minutes after exercise and for every 5 minutes thereafter, up to 30 minutes or until no further resistance increase was observed. Finally, the children were given 0.3 mg of salbutamol using a Ventoline Evohaler with a Babyhaler spacer device (Glaxo Wellcome Production, Evreux, France), and an impulse oscillometry test was performed 15 minutes after the administration of the salbutamol.

An increase in resistance at 5 Hz $\geq 40\%$ was considered evidence of EIB, and a $\geq 40\%$ decrease of resistance at 5 Hz was considered a significant bronchodilator response.^{10,31} The running distance in the hospital was documented in 30 of the 42 children at baseline and during Visits 2 and 3.

Treatment response

The positive response to ICS treatment was defined as a child scoring >19 points on the C-ACT and no significant hyperreactivity were observed on the third visit.

Statistics

For statistics, SPSS Version 22 (IBM Corp, Armonk, NY, USA) was used. For continuous data, the Student's t-test and the Mann–Whitney U test were used, as appropriate. For categorical data, the Chi-square test and Fisher's exact test were used if the number was under 5, and the Mann–Whitney U test was used for comparison between the groups, namely, children under 5 years and those 5 years and older. For comparisons between different time points, the Wilcoxon signed-rank test and Friedman's two-way analysis of variance by ranks were used for continuous data. McNemar's test and Cochran's Q test were used for categorical data.

Ethics

The Helsinki University Hospital of Children and Adolescents Ethics Committee approved the study, and each participant and their guardian provided written, informed assent or consent, as appropriate. The study was registered at clinicaltrials.gov (NCT03377192).

Results

Subject characteristics

The median age of the 42 children (74% boys) who were included in the analysis was 5.3 years (range 4.0–7.9 years), and eleven (26%) had used inhaled steroids in the past six months. Of the 42 children, twelve (29%) had doctor-diagnosed allergic rhinitis and 29 (69%) had doctor-diagnosed atopic dermatitis. We found that 17 (41%) of the children had parents who had been diagnosed with asthma. In addition, 28 (67%) of the children had experienced previous doctor-diagnosed wheezing episodes. The median number of episodes was two, ranging from zero to more than five. The majority of children (74%) were sensitized to aeroallergens (Table 1).

After the baseline visit, every child began regular inhaled steroid treatment. The majority of the children (31 of 42) began taking the Flixotide evohaler (Glaxo Wellcome Production, Evreux, France), which provides 125 mcg 1x2 fluticasone. The other eleven children used a Budesonid Easyhaler (Orion Pharma, Espoo, Finland), which provides 100–200 mcg 1x2 budesonide. Two children were prescribed a long-acting beta2 agonist and ICS at Visit 2: one received Symbicort (AstraZeneca AB, Södertelje, Sweden), which delivers a 4.5/160 mcg dose of formoterol and budesonide, and the other received a Bufomix Easyhaler (Orion Pharma), which delivers a 4.5/160 mcg dose of formoterol and budesonide. Two others were also prescribed a 4–5 mg dose of montelukast.

BHR and lung function

The proportion of children with significant EIB was significantly reduced after the baseline visit (93% vs. 9.5% vs. 9.5%, $p < .001$), and the median increase after exercise with 5 Hz resistance was significantly reduced at Visits 2 and 3 as compared to baseline. There were no differences between Visits 2 and 3 (Figure 2A). The proportion of children with a

significant improvement in bronchodilatation test results was reduced between Visits 1 and 2 and between Visits 1 and 3 (17% vs. 0%, $p = .011$): however, no significant change was observed when the analyses used the median change in bronchodilatation test results between visits (Figure 2B).

Most children already had a normal Z-score value of $<+1.65$ at baseline, and only 6 of 42 children (14%) had an obstruction at their first visit. The proportion of patients with obstructive lung function at baseline was reduced when comparing the baseline visit to Visits 2 and 3 (14% vs. 9.5% vs. 0.0%, $p = .030$). However, no significant improvements in lung function were observed during the study when the analyses used the median change in values (Table 2).

Clinical improvement during ICS treatment

At baseline, the median C-ACT score was 21 (range 11–27). There was significant improvement in the median scores between Visits 1 and 2: 21 (11–27) vs. 24 (20–27), $p < .001$ and between Visits 1 and 3: 21 (11–27) vs. 24 (20–27), $p < .001$, respectively. No significant improvements were noted between Visits 2 and 3 (Figure 2C). In addition, the percentage of children who had a minimum C-ACT score of 22 points was significantly increased between Visits 1 and 3 (43% vs. 88%, $p = .007$) and Visits 1 and 2 (43% vs. 79%, $p = .011$), but not between Visits 2 and 3.

Physiological performance was evaluated by running a distance in 6 minutes. All running-distance data were available for 30 children in the hospital. There were significant improvements in running distance between Visits 1 and 2: 800 m (600–900 m) vs. 850 m (500–1,000 m), $p = .006$. The same was true for Visits 1 and 3: 800 m (600–900 m) vs. 850 m (700–1,050 m), $p = .001$. However, this was not the case between Visits 2 and 3 ($p = .193$; Figure 2D).

Doctor-diagnosed acute wheezing episodes were significantly decreased when they were compared six months before and after ICS treatment: eight of 42 children (19%) vs. 0 of 42 children (0%; $p = .005$). Acute emergency department visits due to any respiratory symptoms also decreased significantly, with the proportion of children having a minimum of one visit decreasing from 19 of 42 (45%) to 5 of 42 (12%; $p < .001$).

There were no side effects from using ICS. The growth in height based on the national Finnish SD curve was stable at -0.4 SD at the start of treatment and -0.2 SD at the third visit ($p = .132$). There were no changes in the weight curve.

Treatment response to ICS

At Visit 3, all 42 children achieved ≥ 19 points in their C-ACT, and 38 of 42 (90%) had no significant hyperreactivity during FRT. Only four children did not respond to ICS. However, two of the four experienced a hyperreactivity reduction of $>50\%$ as compared to the baseline visit.

Eosinophil level

Eosinophil level had no correlation to baseline lung function assessed as the resistance at 5Hz ($R_s = 0.043$), difference in resistance at 5Hz to 20Hz ($R_s = -0.004$), BHR assessed as the increase in resistance at 5Hz ($R_s = -0.193$), or the improvement in R5 after the bronchodilation test ($R_s = -0.133$). However, children who responded to ICS had higher eosinophils compared to the non-responders ($Md = 0.60$ vs 0.14 , $p = .029$).

Patients without aeroallergen sensitization

We found that eleven of 42 (26%) children had no aeroallergen sensitization. Those 11 children were identical to the others with respect to their age, sex distribution, parental asthma history, parental smoking habits, and having a furry animal at home. In total, ten of

these eleven children demonstrated a $\geq 40\%$ increase in resistance at 5 Hz after exercise at baseline, and this fell significantly to three children at Visit 2 and two children at Visit 3 ($p = .004$). We also saw a similar decrease in resistance at 5 Hz after exercise ($p = .025$) among sensitized children (Figure 3A).

Non-sensitized children showed a significant improvement in their C-ACT scores at the three visits (20 vs. 23 vs. 24 points, $p = .034$; Figure 3B), which was similar to sensitized children. There were no significant changes in physical performance on the FRT ($p = .093$; Figure 3C). In the six months before the study, one of the eleven children had a doctor-diagnosed wheezing episode, but there were no wheezing episodes in the six months after the study began ($p > .05$).

Findings in children under 5 years of age

In terms of baseline characteristics, the only significant difference between age groups was that one of 16 children (6.3%) under 5 years had a furry animal at home, and ten of 26 (38.0%) of the older children did ($p = .030$). There were no differences in sex, atopy status, previous asthma diagnoses, parental asthma, or parental smoking.

Similar to the older children, the 16 children under five years of age showed significant improvements in the change in resistance at 5 Hz after exercise (Figure 4A), C-ACT test scores from the baseline to Visits 2 and 3 ($p = .002$; Figure 4B), and physical performance in the 6-minute running test ($p = .002$; Figure 4C).

Discussion

Our study has three main findings. First, over 90% of all children responded to ICS treatment in terms of improving C-ACT scores, decreasing acute doctors' visits, and decreasing EIB, measured as the resistance change at 5 Hz after exercise. Second, children improved their physical performance within six weeks of starting ICS treatment. Third, children under five years of age and children without allergic sensitization also benefited from ICS treatment, suggesting that the 6-minute FRT and impulse oscillometry can aid in treatment decisions and represents a useful tool in evaluating children with suspected asthma.

Without objective testing there is a risk of over-diagnosing and misdiagnosing asthma and over-treating ICS, which is why objective testing is needed.^{32,33} The highest proportion of childhood asthma in birth cohorts has reached over 40%, implying the overdiagnosis of asthma.¹ Impulse oscillometry can be used beginning at the age of 2 years, according to ERS.⁹ In previous studies, impulse oscillometry predicted baseline lung function in spirometry in school-age children,³⁴ and impulse oscillometry in pre-school aged children predicted lung function in adolescence.⁷ Also, preschool-aged children with asthma had pronounced bronchodilator responsiveness as compared to healthy controls.⁶ Moreover, impulse oscillometric variables linked to small airway function (such as the frequency dependence of resistance or reactance area) have been found to be associated with a loss of asthma control and the severity of asthma.^{35, 36, 37} However, there are few studies characterizing inhaled corticosteroid treatment responses that use impulse oscillometry.

Most of our patients (31/42) were boys with aeroallergen sensitization, which fits well with the natural history of childhood asthma and allergies.^{38, 39} Only seven of 42 children had no eosinophilia or aeroallergen sensitization. Also, a majority of the children had previous viral-induced wheezing episodes in early childhood.

The vast majority of children examined here responded to ICS treatment, unlike in many previous studies,^{25, 26} implying the value of impulse oscillometry in identifying responders to ICS treatment. Also, in cases where child has symptoms despite ICS-treatment, monitoring with oscillometry and FRT may be useful to avoid overtreatment.

Our study showed no significant improvement in lung function when median Z-score values were used, unlike a study of children aged 5–12 years.²² However, after ICS treatment, none of the 42 children had obstructive baseline oscillometry at the third visit as compared to six of the 42 children before the treatment. BHR, as measured by the indirect provocation test, an exercise-induced increase in respiratory resistance, was significantly reduced in 5–6 weeks after the start of ICS. This also fit well with previous studies conducted on older school-age children.^{10,11, 20–22} In our previous study,²³ no significant change in BHR was observed when it was measured using the hypertonic saline challenge.

There was a clear clinical improvement among the children. The C-ACT improved significantly after 5–6 weeks of ICS treatment. This fits well with previous studies.^{23, 24} Also, ICS treatment significantly reduced acute doctors' visits six months before and six months after starting the medication, as previous studies have shown in preschool children.^{25, 40}

Physical performance significantly improved by 50 meters (6.3%) in the FRT in 5–6 weeks after the start of ICS. The age-related mean improvement in the same running test in the same place for children aged 7–8 years was 38 m, according to research by our team (unpublished data), implying that the increase was significant. In addition, in another study of more than 1 million children, improvements among children 9–10 years of age on the 20 m shuttle run test were 3.3% for boys and 3.8% for girls;⁴¹ this also suggests the significance of our finding and that ageing was not the reason for improved performance. As far as we know,

this kind of improvement after ICS treatment has not been reported in any published paper on preschool-age children.

Children without allergic sensitization improved clinically, and BHR decreased similarly to other children. Traditionally, those children have been considered to have a poor response to ICS.^{14, 15} In addition, children under five years of age had similar results as compared to older children. This suggests that the classification of childhood asthma could possibly be rethought. For example, children aged 4–11 years could possibly be treated as one group in the asthma guidelines.

The strength of the study was that most of the diagnoses were based on both the patients' clinical histories and their objective BHR results on the lung function test. This is probably a major reason that the results were so positive and most of the children responded well to ICS treatment. However, the study had certain limitations. The vast majority of the patients did not have their FeNO measured, because the examination often failed. Noting the change in FeNO would have offered information about how to get inflammation under control. This was a follow-up study, so we did not have a control group. For four of 42 children, clinical treatment changed during the observation period. However, the vast majority of the children were treated with aerosol fluticasone.

In conclusion, impulse oscillometry combined with FRT is a useful tool for identifying asthma in young children. Children with asthmatic symptoms who demonstrate objective BHR during the FRT should be treated with ICS, regardless of their atopy status. Further studies with larger numbers of children without eosinophilia or aeroallergen sensitization are needed. These should evaluate whether the 6-minute FRT with impulse oscillometry indicates an independent clinical phenotype of young children who benefit from ICS treatment.

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Figure 1. Flow chart of the study. C-ACT, childhood asthma control test; FRT, 6-minute FRT.

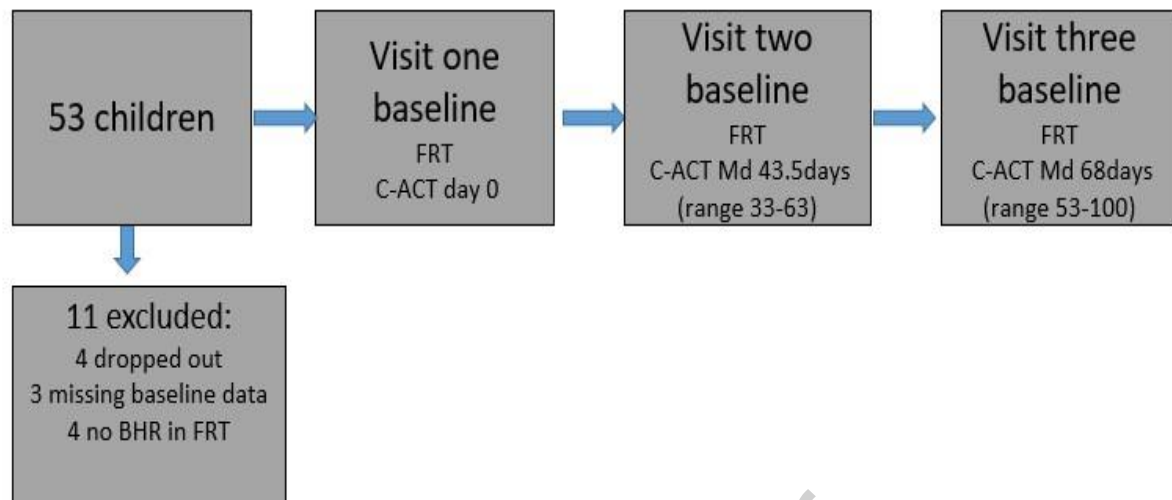


Figure 2A. Percentage change in resistance at 5 Hz after exercise for 40 children who performed the running test at every visit. *** $p < .001$ compared to Visit 1.

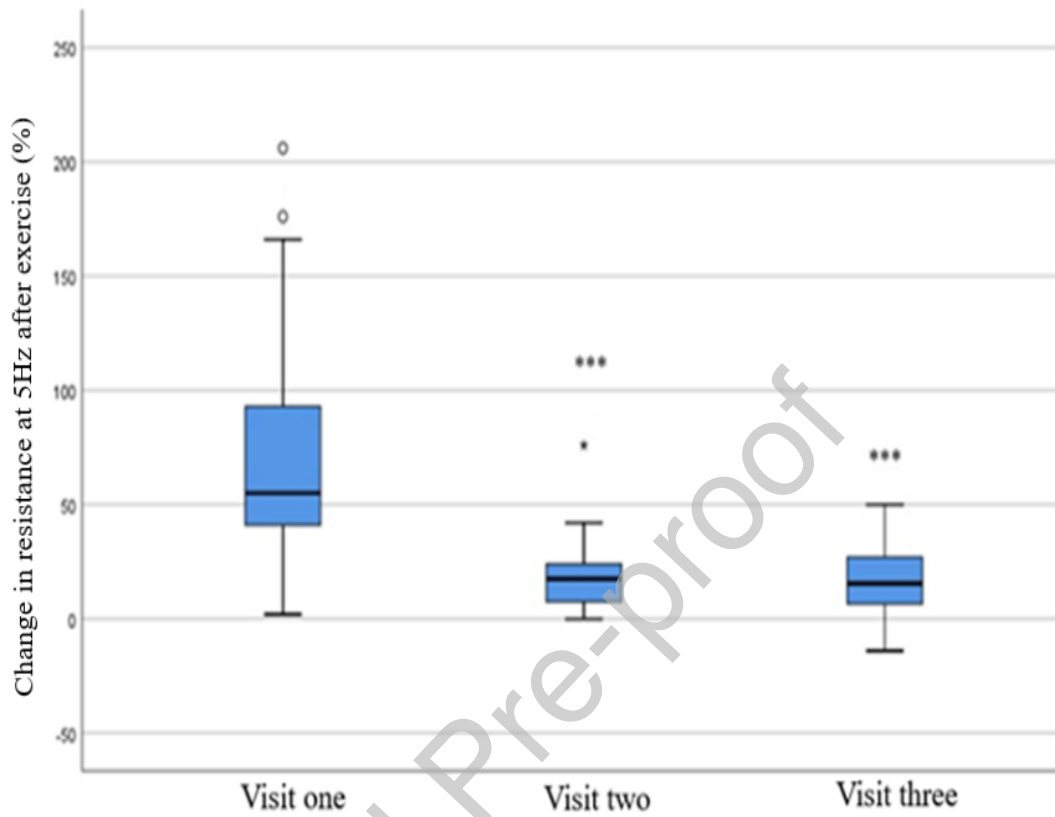


Figure 2B. Percentage change in resistance at 5 Hz after bronchodilatation test for 42 children.

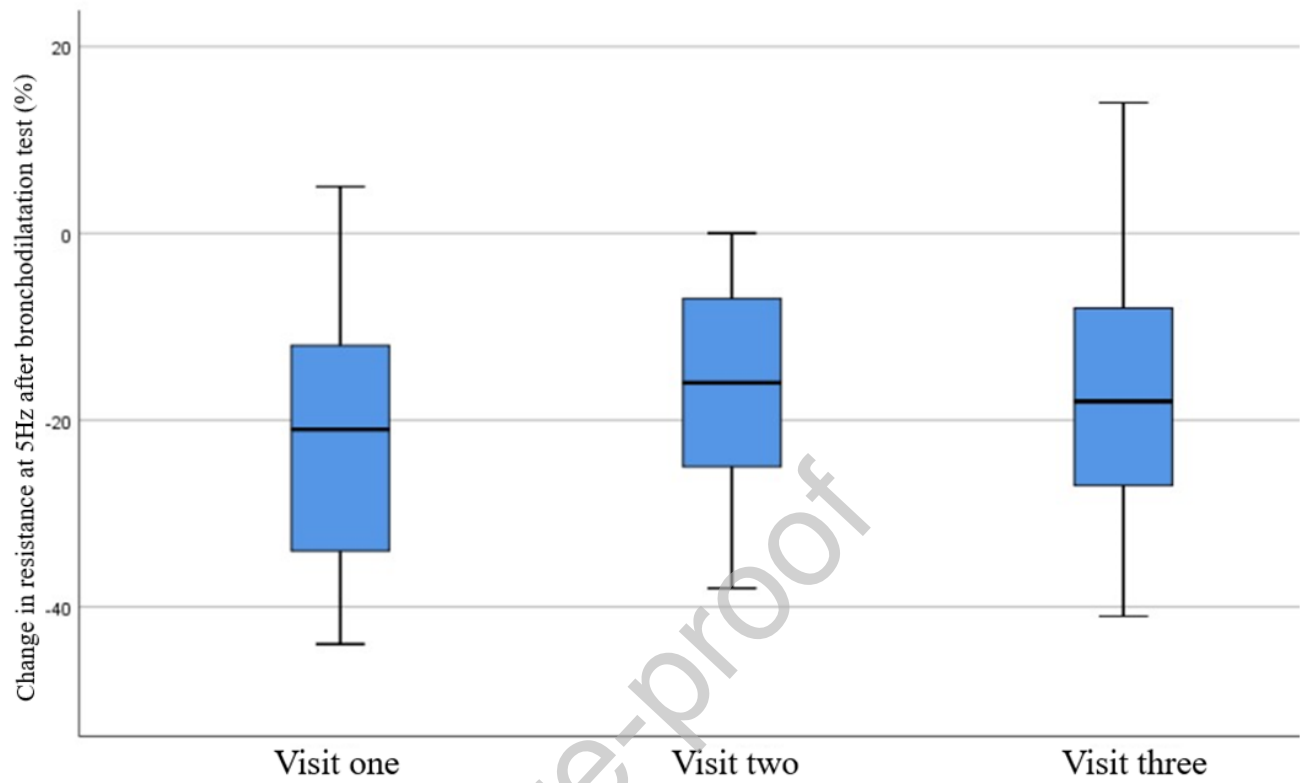


Figure 2C. Childhood asthma test scores at the three visits for 42 children. *** $p < .001$ compared to Visit 1.

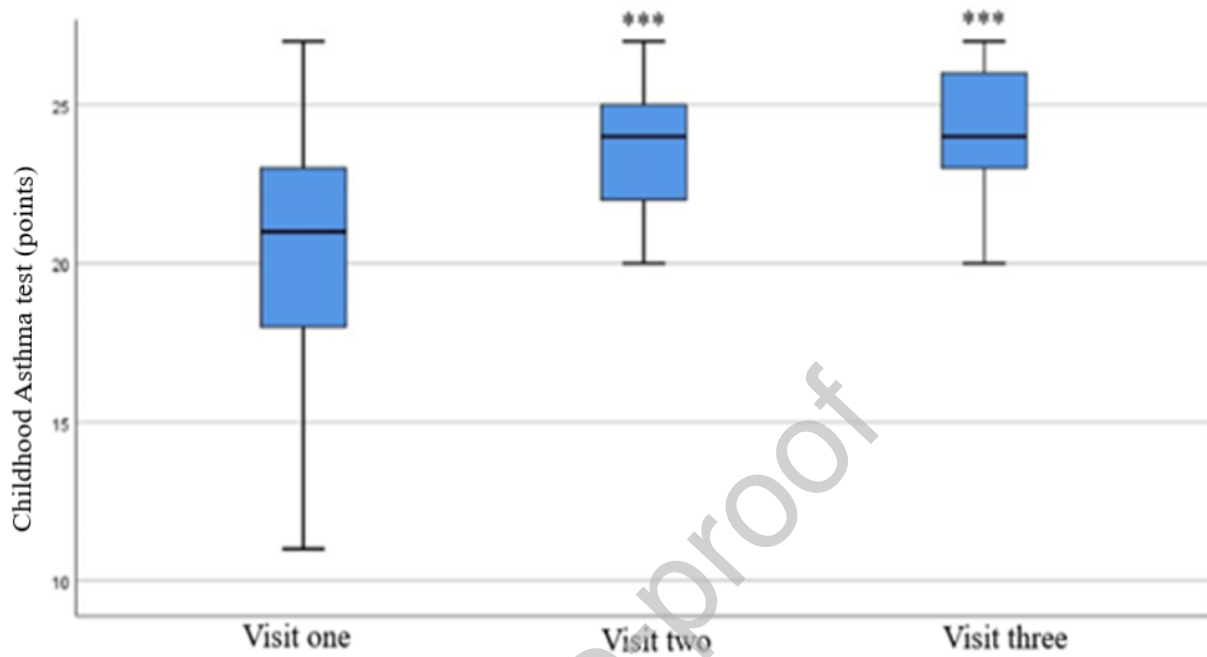


Figure 2D. Running distance at the three visits for 30 children. ** $p < .01$ compared to Visit 1. *** $p < .001$ compared to Visit 1.

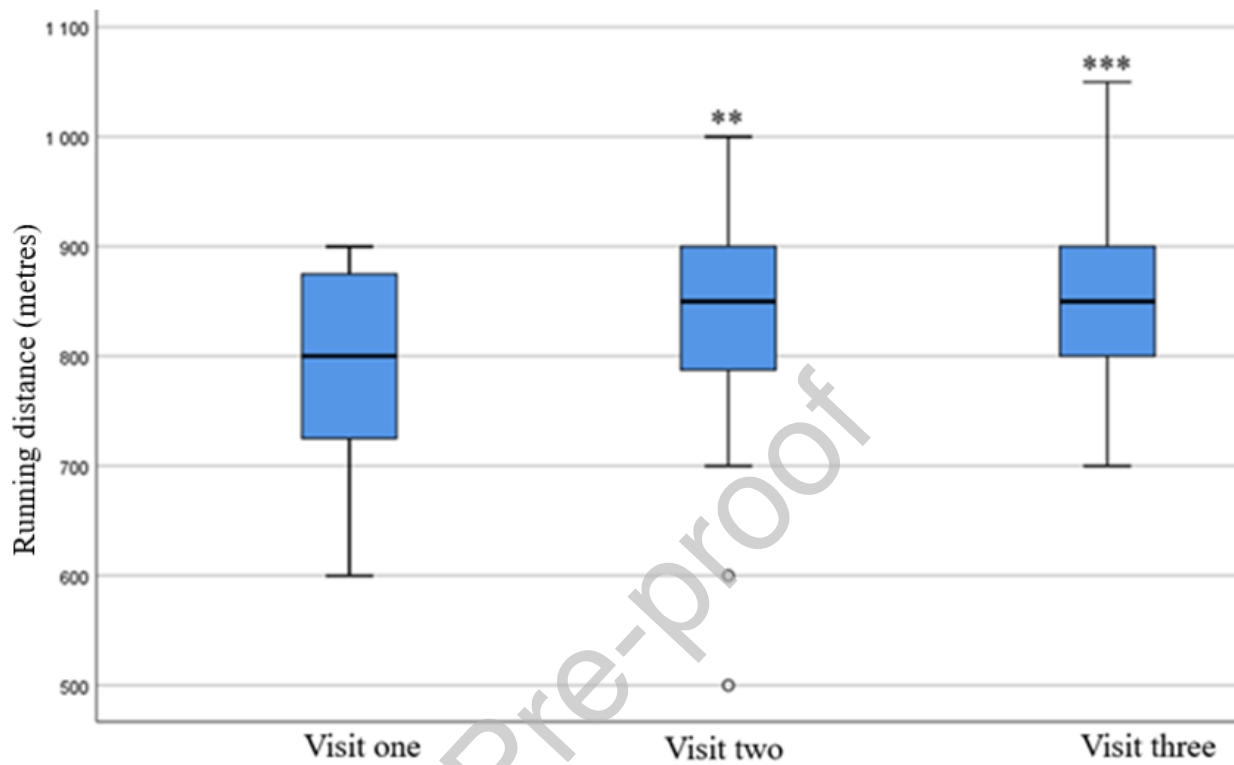


Figure 3A. The percentage change in resistance at 5 Hz after exercise in 10 children without, and 30 children with, aeroallergen sensitization. *** $p < .001$ compared to the baseline. * $p < .05$ compared to Visit 1.

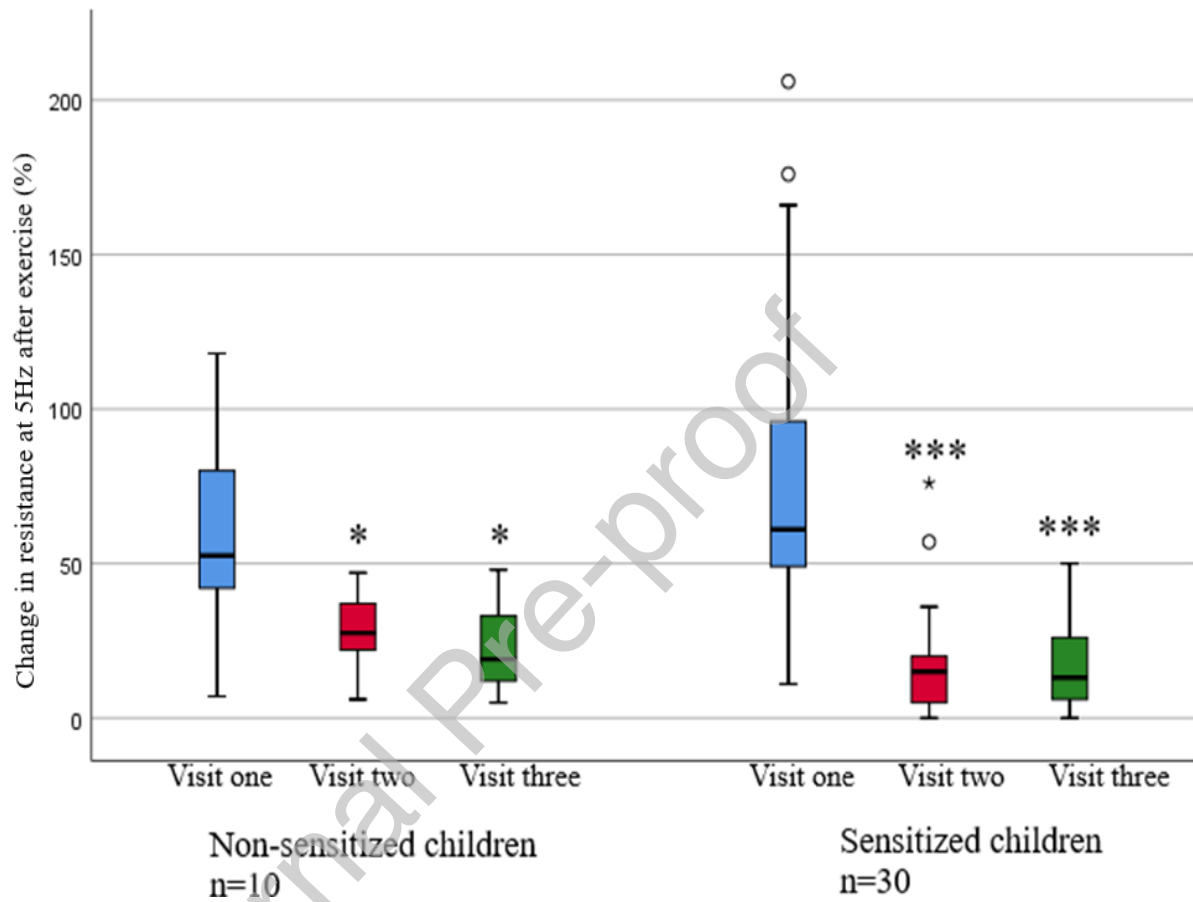


Figure 3B. Childhood asthma test scores at the three visits in 11 children without, and 31 with, aeroallergen sensitization. * $p < .05$ compared to Visit 1. *** $p < .001$ compared to Visit 1.

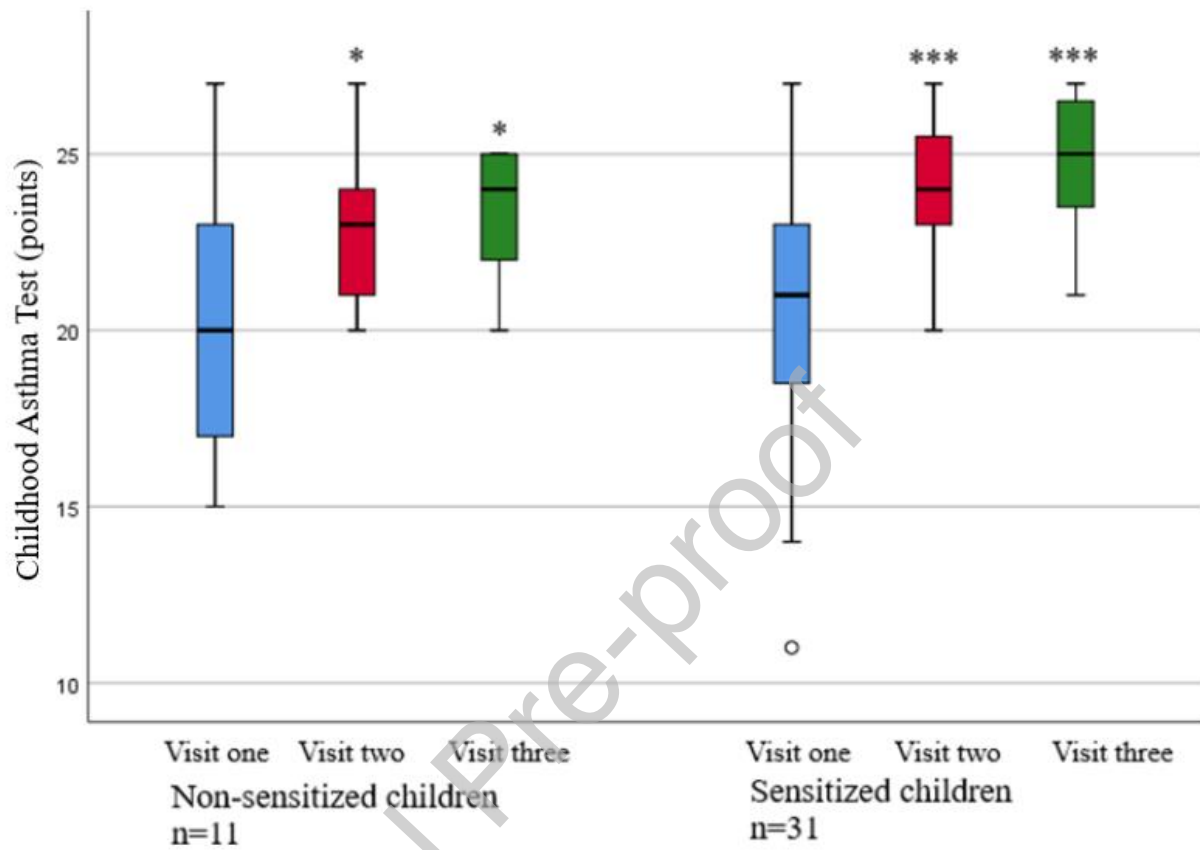


Figure 3C. Running distance in meters at the three visits for eight children without, and 22 with, aeroallergen sensitization. ** $p < .01$ compared to the baseline.

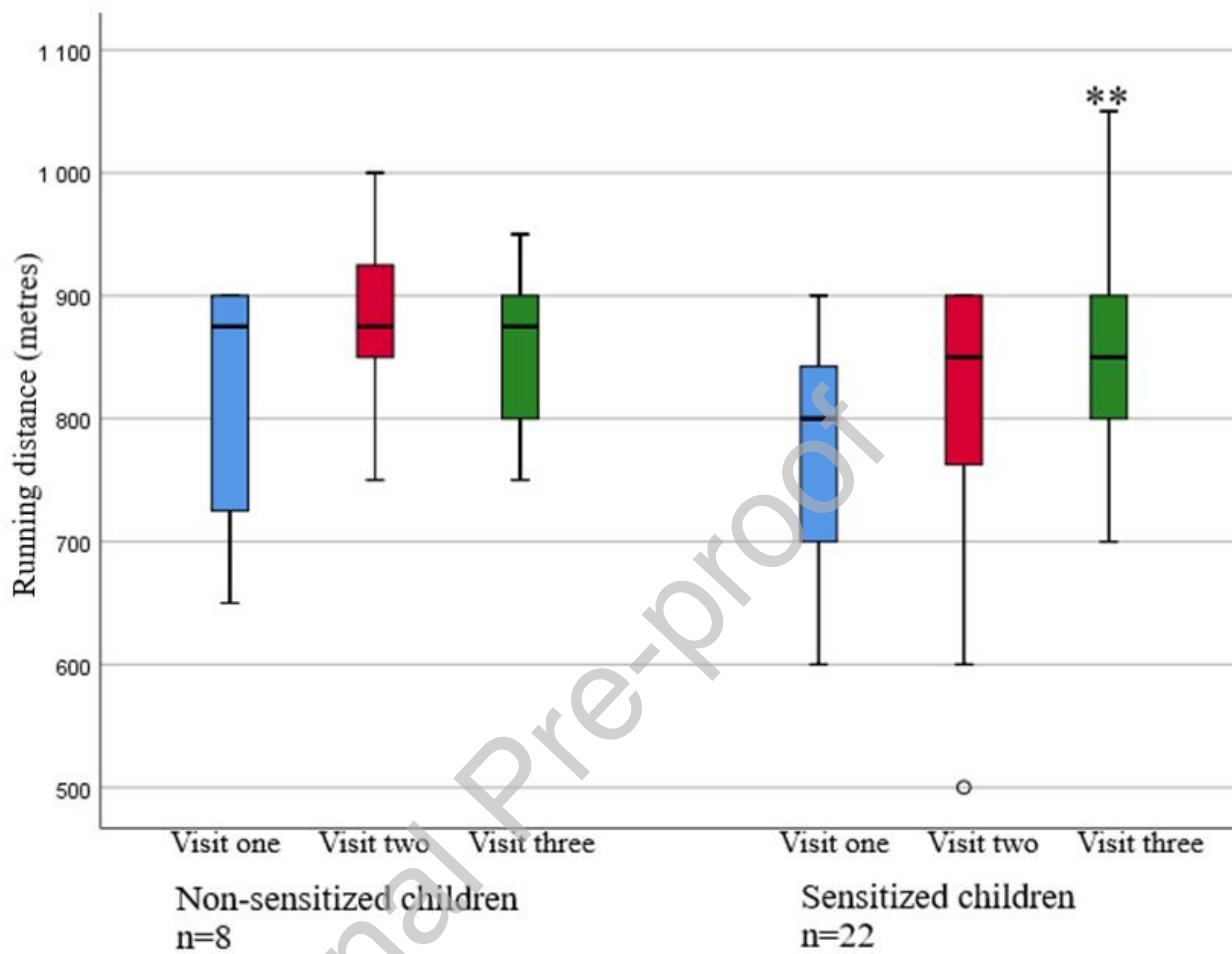


Figure 4A. Percentage change in resistance at 5 Hz after the 6-minute FRT for 15 of 16 children under 5 years of age, compared to the baseline. *** $p < .001$ compared to Visit 1.

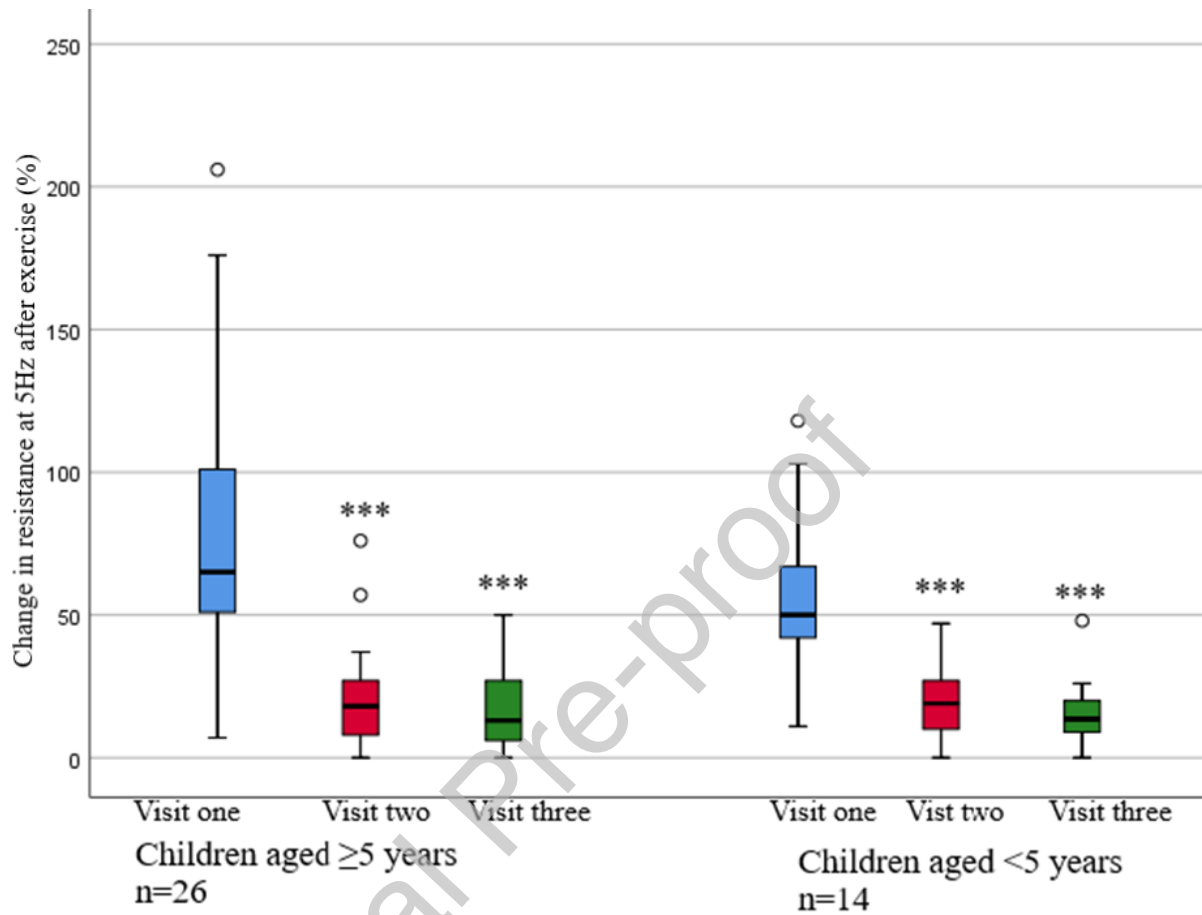


Figure 4B. Childhood asthma test points at the three visits for the 16 children aged less than 5 years and the 26 children aged 5 years and older at the start of the study. ** $p < .01$ compared to Visit 1. *** $p < .001$ compared to Visit 1.

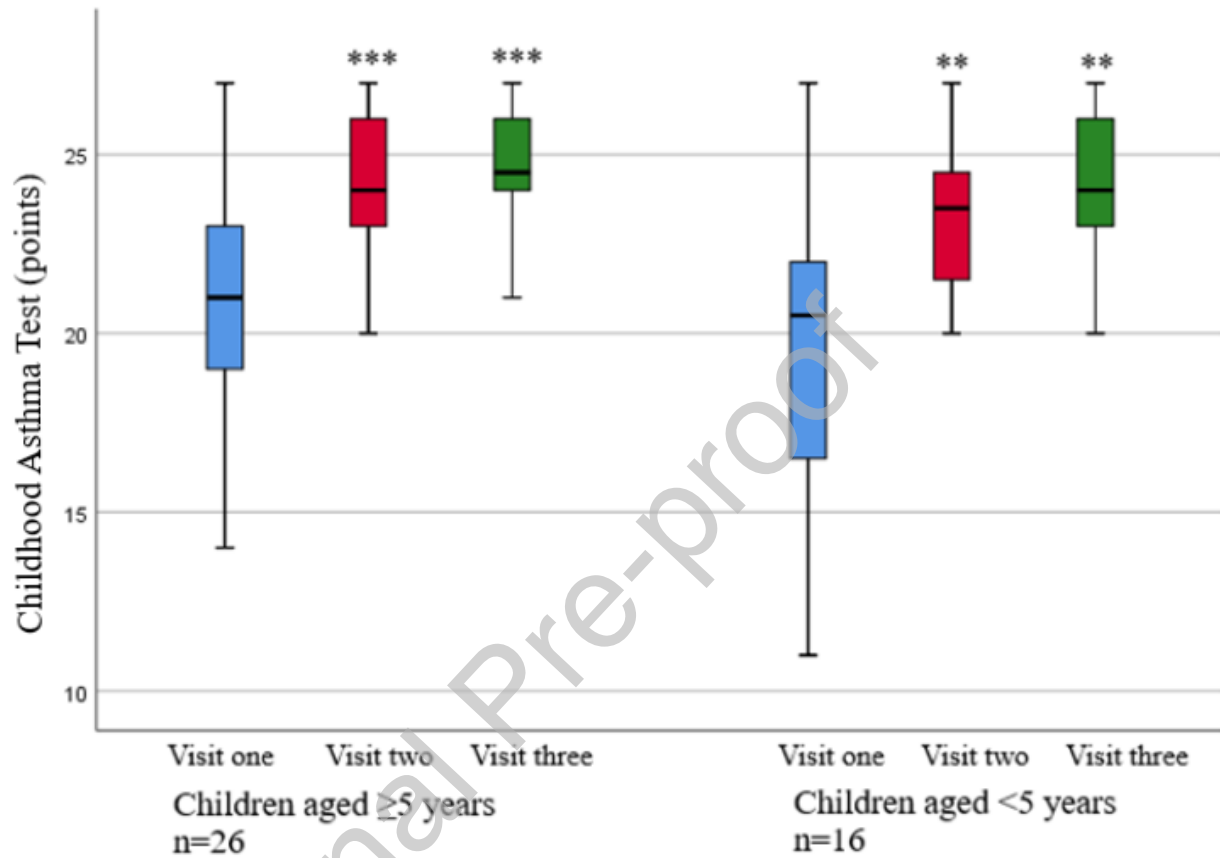


Figure 4C. Running distance achieved in the 6-minute FRT by the 11 children aged less than 5 years and the 19 children aged 5 years and older at the start of the study. * $p < .05$ compared to Visit 1. ** $p < .01$ compared to Visit 1.

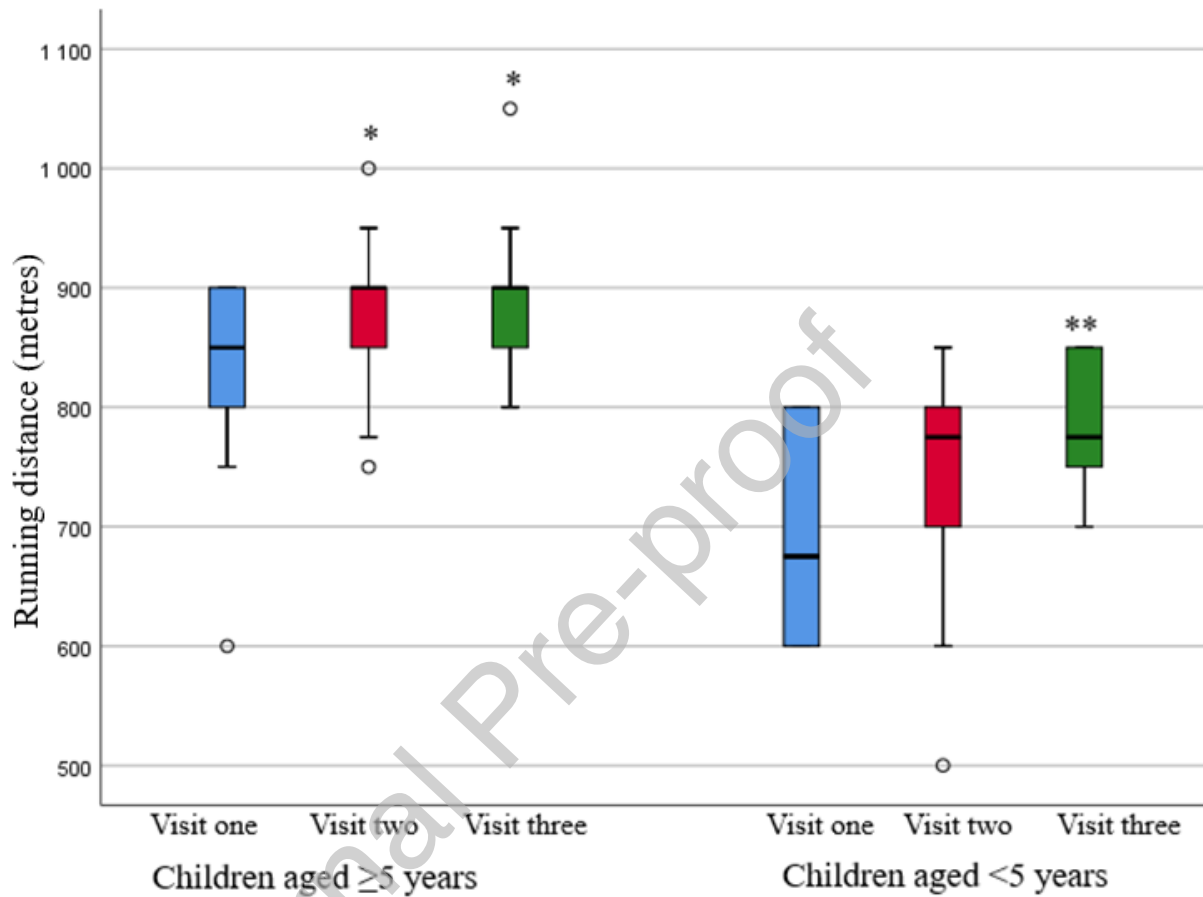


Table 1. Baseline characteristics of the 42 children

Variable	Children, < 5 years (n=16)	Children, ≥ 5 years (n=26)	Total (n=42)
Age (years), median, range	4.7 (4.0–4.9)	5.9 (5.0–7.9)	5.3 (4.0–7.9)
Sex (boys)	12 (75)	19 (73)	31 (74)
Previous asthma diagnosis in childhood	7 (44)	9 (35)	16 (38)
Regular asthma medication in past six months	3 (19)	8 (31)	11 (26)
Doctor-diagnosed allergic rhinitis	3 (19)	9 (35)	12 (29)
Doctor-diagnosed atopic dermatitis	12 (75)	17 (65)	29 (69)
Parental asthma	9 (56)	8 (31)	17 (41)
Parental smoking	4 (25)	6 (23)	10 (24)
Doctor-diagnosed wheezing episodes at any point	13 (81)	15 (58)	28 (67)
Number of doctor-diagnosed wheezing episodes	3 (0, ≥5)	1 (0, ≥5)	2 (0, >5)
Furry animal at home	1 (6.3)	10 (38)	11 (26)
Sensitization to aeroallergens	11 (69)	20 (77)	31 (74)

Note: Data are presented as median and range or n (%).

Table 2. Lung function measurements for the 42 children

Variable	Visit 1 (n=42)	Visit 2 (n=42)	Visit 3 (n=42)	P-value
Resistance at 5 Hz, Z-score (SD)	+0.15 (1.38)	-0.18 (1.34)	-0.22 (1.18)	.218
Resistance at 20 Hz, Z-score (SD)	-0.67 (1.12)	-1.86 (0.89)	-1.70 (1.12)	.001
Reactance at 5 Hz, Z-score (SD)	-1.72 (2.91)	-2.78 (3.61)	-1.79 (2.37)	.017
Difference in resistance at 5 Hz and 20 Hz, Z-score (SD)	+1.07 (1.83)	+1.93 (2.02)	+1.46 (1.52)	.009
Obstruction ^a in impulse oscillometry	6 (14%)	4 (9.5%)	0 (0.0%)	.030
BHR*	42 (100%)	4 (9.5%)	4 (9.5%)	.001

^a Defined as $\geq +1.65$ SD in resistance at 5 Hz; *Defined as $\geq 40\%$ in resistance at 5 Hz after exercise, or decrease of $\geq 40\%$ compared to baseline in the bronchodilatation test. Friedman's two-way analysis of variance by ranks was used for continuous data. McNemar's test and Cochran's Q test were used for categorical data.