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BMI predicts exercise induced bronchoconstriction in asthmatic boys

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Abstract

Background: Exercise induced bronchoconstriction (EIB) is a frustrating morbidity of asthma in children. Obesity has been associated with asthma and with more severe EIB in asthmatic children.

Objectives: To quantify the effect of BMI on the risk of the occurrence of EIB in children with asthma.

Methods: Data were collected from six studies in which exercise challenge tests were performed according to international guidelines. We included 212 Children aged 7-18 years, with a pediatrician-diagnosed mild-to-moderate asthma.

Results: A total of 103 of 212 children (49%) had a positive exercise challenge (fall of $FEV_1 \geq 13\%$). The severity of EIB, as measured by the maximum fall in FEV_1, was significantly greater in overweight and obese children compared to normal weight children (respectively 23.9% vs 17.9%; $P = 0.045$). Asthmatic children with a BMI *z*-score around +1 had a 2.9-fold higher risk of the prevalence of EIB compared to children with a BMI *z*-score around the mean (OR 2.9; 95%CI: 1.3-6.1; $P < 0.01$). An increase in BMI *z*-score of 0.1 in boys led to a 1.4-fold increased risk of EIB (OR 1.4; 95%CI: 1.0-1.9; $P = 0.03$). A reduction in pre-exercise FEV_1 was associated with a higher risk of EIB (last quartile six times higher risk compared to highest quartile (OR 6.1 [95%CI 2.5-14.5]).

Conclusions: The severity of EIB is significantly greater in children with overweight and obesity compared to non-overweight asthmatic children. Furthermore, this study shows that the BMI-*z*-score, even with a normal weight, is strongly associated with the incidence of EIB in asthmatic boys.

KEYWORDS
adolescent, asthma, children, obesity

1 | INTRODUCTION

Exercise induced bronchoconstriction (EIB) is a common manifestation of asthma in children, and defined as the transient narrowing of the airways occurring during or after vigorous exercise.[1,2] Asthma can have a detrimental impact on physical activity in children.[3] Dropping-out of play and sports may lead to reluctance to participate or avoidance of exercise, which can reduce quality of life.[3,4]

Obese children are less tolerant of weight baring exercise compared to peers as their maximum oxygen uptake per kilogram body weight is usually lower, limiting athletic performance. Obesity has also been associated with asthma[5,6] and with more severe EIB in asthmatic children,[7] although the prevalence of EIB does not seem to differ.[7,8] This makes sense as overweight increases (at any workload) the level of ventilation, which is the exact stimulus for the severity of EIB. So less body weight will result in less severe EIB. Van Leeuwen et al showed in a prospective study that even a small reduction in BMI reduced EIB at group level in asthmatic overweight children.[9] In asthmatic children who are not overweight, the relationship of body mass index (BMI) and EIB is yet to be determined, although far below average children had a lower incidence of EIB.[10]

A pre-exercise obstructive flow volume curve was related to the prevalence of EIB in asthmatic children,[11] however. others could not find a relation between pre-exercise spirometry and EIB.[12,13]

The aim of this study was to investigate the relation of BMI and pre-exercise FEV_1 on occurrence and severity of EIB in asthmatic children, by pooled data of six studies performed in our study center.

2 | METHODS

2.1 | Types of studies

Data were collected from six studies with exercise challenge tests performed by the department of pediatrics, Medisch Spectrum Twente, Enschede, the Netherlands, between 2005 and 2011.[2,9,14–17]

2.2 | Subjects

Children aged 7-18 years, with a pediatrician-diagnosed mild-to-moderate asthma were evaluated for EIB and recruited from the outpatient clinic of the pediatric department of Medisch Spectrum Twente. Children were included if they had clinical stable asthma (ie, no hospital admissions or use of systemic corticosteroids 3 weeks prior to the study), with a forced expiratory volume in 1 s (FEV_1) predicted of ≥70% at baseline, no pulmonary or cardiac co-morbidity and a technical correct flow-volume curve.

Children and their parents received written patient information and signed an informed consent form before study entry, and trials were entered at IRCTN (ISRCTN61380683, ISRCTN90761040), and trialregister.nl (NTR2045).

2.3 | Spirometric measurements

Pulmonary function tests were performed using a standardized protocol according to international guidelines.[18] After exercise spirometric measurements were performed in duplo. A Masterscope® Jaeger® (Germany) was used prior to April 2008 and after April 2008 a Microloop® MK8 Spirometer (UK) with Spida5® software was used to measure flow-volume loops.

Pre-exercise FEV_1 was expressed as a percentage of the predicted value. Children did not use short-acting bronchodilators within 8 h and long-acting bronchodilators within 24 h prior to testing.

2.4 | Exercise challenge test

Exercise challenges were performed by running with nose clipped on a treadmill with a 10% incline using the standardized ATS protocol.[19] Exercise challenges were performed in the local skating rink (www.ijsbaan-twente.nl), to obtain cold, dry air (1-10°C; humidity 1.0-6.0 mg $H_2O \cdot L^{-1}$). During the test, heart rate was continuously monitored. Children ran for a total of 6 min, with a 2-min period to reach the targeted heart rate of 80-90% of predicted maximum (210-age).[20] Spirometry was obtained before exercise and at 1, 3, 6, 9, 12, 15, and 20 min after exercise. EIB was defined as a fall of ≥13% from baseline.[21–23] An increase of FEV_1 after exercise was noted as a fall of 0% from baseline, as these children did not have EIB. The maximum fall in FEV_1 compared to baseline was used for analysis (as the severity of EIB).

2.5 | Statistics analysis

Continuous data were all normally distributed and expressed as mean values ± standard deviation (SD). Categorical data were expressed as numbers with corresponding percentages.

BMI was adjusted for age and gender and calculated as standard deviation (BMI *z*-score), according to the Fifth Dutch Growth Study.[24,25] International age- and gender-related cut off points from Cole et al were used to determine if children were overweight or obese.[24]

Differences between groups were analyzed with a *T*-test for continuous variables and a χ^2 test for categorical variables. Variables that were associated with EIB with a significance at or below $P = 0.15$ were considered candidate variables for multivariate logistic regression analysis and were all entered. Subsequently, variables with the highest *P*-value were eliminated step by step until the fit of the model decreased significantly (based on −2 log likelihood). Correlation between baseline FEV_1 and BMI *z*-score or maximum fall in FEV_1 after exercise were calculated using Pearson correlation. The same tests were used for analyzing gender specific outcomes. Children with a BMI between 0 and +1 SD were analyzed separately, because the regular patient will fit in this group.

A two-sided value of $P < 0.05$ was considered statistically significant. All analyses were performed with SPSS® for Windows version 20 (IBM, Chicago, IL).

3 | RESULTS

3.1 | Patient characteristics and EIB prevalence

Two hundred and twelve children (age 12.6, ±2.4 years) with a history of mild-moderate asthma performed an ECT in cold air. Forty Children (19%) were overweight and 10 children were obese (5%).

When setting the threshold for EIB at a fall in FEV_1 of 13%, 103 of 212 children (49%) had a positive exercise challenge. Age, sex distribution, use of inhaled corticosteroids, and temperature of test environment did not differ significantly among children with and without EIB.

3.2 | BMI and prevalence of EIB

Asthmatic children with EIB had a higher BMI *z*-score compared to children without EIB (Table 1). In the multivariate logistic regression model, an increase in BMI *z*-score of 0.1 led to a 1.04-fold increased risk of EIB (OR 1.04; 95%CI: 1.0-1.1; $P = 0.003$).

Specified for gender, there was only a significant difference in BMI *z*-score between boys with and without EIB (Table 1) and no significant difference for girls.

Asthmatic children with a BMI *z*-score between 0.5 and 1.5, had a 2.9-fold increased risk of the incidence of EIB, compared to children with a BMI *z*-score between −0.5 and 0.5 (Odds ratio [OR] 2.9; 95%CI: 1.3-6.1; Fig. 1). In exploratory analyses, the increased risk for boys between these BMI *z*-scores intervals was 4.4-fold (OR 4.4; 95%CI 1.5-12.7).

3.3 | Prevalence of EIB specified for gender

Using a multivariate logistic regression model for boys with a BMI *z*-score between 0 and +1 SD, BMI *z*-score and pre-exercise FEV_1 were the best independent predictors of the occurrence of EIB. An increase in BMI *z*-score of 0.1 led to a 1.4-fold increased risk of EIB (OR 1.4; 95% CI: 1.0-1.9). Since there was no linear relationship between pre-exercise FEV_1 and the occurrence of EIB, we divided FEV_1 in two groups and used the highest group (above the median) as reference group. Boys in the lower group had a 11 times higher risk of the occurrence of EIB compared to children in the higher group (OR 11.1 [95%CI 2.4-51.4]).

No independent predictor of the occurrence of EIB was detected in girls with a BMI *z*-score between 0 and +1 SD.

3.4 | BMI and severity of EIB

The severity of EIB, as measured by the maximum fall in FEV_1, was significantly greater in the group with overweight and obese children than in the normal weight children (respectively 23.9% vs 17.9%).

3.5 | Pre-exercise FEV_1 and EIB

In both boys and girls there was a significant difference in pre-exercise FEV_1 between children with and without EIB (pre-exercise FEV_1 92.2% for boys with EIB, 100.3% for boys without EIB; and pre-exercise FEV_1 93.8% for girls with EIB, 100.7% without EIB).

In the multivariate logistic regression model, we found that pre-exercise FEV_1 was an independent predictor of the occurrence of EIB. After dividing the group in four quartiles and using the highest quartile as reference group (because lack of a linear relationship), children in the last group had a six times higher risk of the occurrence of EIB compared to children in the highest quartile (OR 6.1 [95%CI 2.5-14.5]). Children in the second-last quartile had an almost significant two times higher risk of EIB (OR 2.2 (95%CI 1.0-4.9; $P = 0.052$). Children in the second-highest quartile had a comparable risk of the occurrence of EIB (OR 0.9 [95%CI 0.4-2.1]).

There was a poor, although statistically significant correlation between pre-exercise $FEV_1$and severity of EIB as measured by maximum fall in FEV_1 ($r = -0.32$).

4 | DISCUSSION

We show that severity of EIB is significantly greater in children with overweight and obesity compared to non-overweight asthmatic children. Furthermore this study shows that the BMI-*z*-score, even with a normal weight, is strongly associated with the incidence of EIB in asthmatic boys.

In line with our observations Baek et al found in a cross-sectional study more severe EIB in obese, compared to normal weighted asthmatic children.[7] In children far below average weight Calvert also observed an association between BMI and EIB.[10] This

TABLE 1 Patients' characteristics

	EIB, *n* = 103	No-EIB, *n* = 109	*P*-value
Gender (% male)	66 (64)	65 (60)	NS
Age (years)	12.6 ± 2.4	12.6 ± 2.4	NS
BMI *z*-score	0.47 ± 1.2	0.16 ± 1.0	0.04
BMI *z*-score girls	0.52 ± 1.02	0.36 ± 0.94	NS
BMI *z*-score boys	0.45 ± 1.24	0.03 ± 1.03	0.04
Overweight or obese[a]	30 (29)	20 (18)	NS
ICS use	66 (64)	76 (70)	NS
Pre-exercise FEV_1 (% predicted)	92.8 ± 13.2	100.5 ± 13.8	0.00

BMI *z*-score, body mass index (SD from adjusted mean); FEV1, forced expiratory volume in 1 s.
Continuous variables are expressed as mean ± SD, categorical variables as number (%).
[a]According international age- and gender-related cut off points for overweight and obesity.

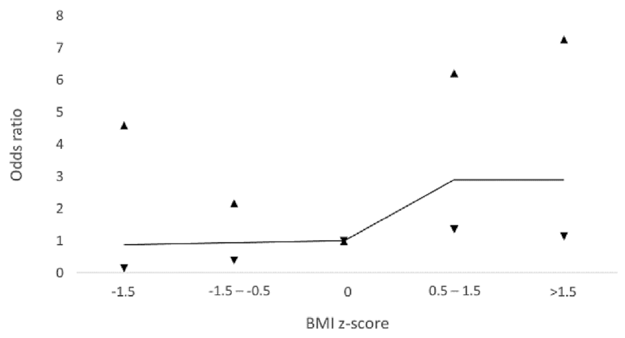

FIGURE 1 Odds ratio's for the different weight groups, the line represents the odds ratio while the dashes triangles represent the upper and lower confidence intervals

corresponds to our study that BMI-*z*-score, both in normal and overweighted asthmatic children weight, is strongly related to EIB. We found that asthmatic children with a BMI *z*-score between 0.5 and 1.5 had a 2.9-fold increased risk of the prevalence of EIB compared to children with a BMI *z*-score around the mean (BMI *z*-score between −0.5 and 0.5). Of our study group, van Leeuwen et al showed in marginally overweight and obese asthmatic children in a prospective study that a relatively small diet-induced reduction of BMI could reduce severity of EIB on group level, further emphasizing the link between BMI and EIB.[9]

Several mechanisms have been suggested for the dose-response association between BMI and asthma: mechanical fat load of truncal adiposity; metabolic dysregulation; obesity-related inflammatory markers like leptin[26]; and more recently airway dysanapsis.[27] EIB is a frequent morbidity in childhood asthma restricting participation in play and sports. Several studies have shown that asthmatic children are less active than their healthy peers which induces waste of muscular mass and buildup of adipose tissues. Whether this leads to a significant shift in BMI or frank overweight is individually dependent on genetics and other variables such as lifestyle. The weak link between pre-exercise FEV1 and EIB and the strong link between BMI *z*-score and EIB we observed, may be the result of airway dysanapsis. This implies a BMI associated anatomical, developmental disorder of the airways preserving FEV_1, but possibly interfering with exercise induced bronchoprotection counterbalancing EIB.[27]

In our study, asthmatic boys with EIB had a significantly and clinically relevant higher BMI compared to boys without EIB (*z*-score 0.45 vs 0.03, $P = 0.04$). Asthmatic girls with EIB, however, did not have a s significantly higher BMI (*z*-score 0.52 vs 0.36, $P = 0.45$).

This is in line with a meta-analysis on the relationship between overweight and incident asthma in childhood of Chen et al, which showed a significantly stronger relationship between BMI *z*-score and asthma in boys, compared to girls.[6] This gender different association between BMI and asthma we observed was also disclosed in the review of Vijayakanthi et al.[28]

We speculate the gender different relation of EIB and BMI may be related to greater EIB induced physical inactivity in asthmatic boys, and/or more truncal fat load, which is more associated with metabolic and inflammatory dysregulation.[26]

This study shows that the pre-exercise FEV_1 has a moderate association with the prevalence of EIB in asthmatic children; only children in the last quartile had a significant increased risk of occurrence of EIB. Other studies did not find a significant association between pre-exercise lung function and EIB[12,13,29,30] indicating that FEV_1 is not a strong predictor of the prevalence of EIB. Linna analyzed pre-exercise flow volume loops and found that an obstructive expiratory loop on visual assessment did predict the prevalence of EIB.[11]

The main strength of our study is the high quality of standardized exercise tests; all ECT's were performed by running on a treadmill using the same conditions in cold, dry air in the local skating rink, markedly increasing the sensitivity of an ECT.[19] Another strength was the large study sample compared to other studies. Weaknesses of our study are the cross-sectional study design and the low number of overweight girls, precluding gender specific analysis of BMI and EIB prevalence in normal weighted asthmatic children. Also, we did not assess pubertal stage, nor body composition, both of which could be important confounders.

5 | CONCLUSION

EIB indicates a poor control of asthma and may lead to a sedentary lifestyle changing BMI and body composition. Clinicians should be aware of the strong relation of BMI *z*-score and EIB even in not overweight asthmatic boys. This study highlights the need for gender-specific prospective studies of the association of BMI and body composition on the one hand and pulmonary function deficits on the other in children with asthma.

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CONFLICTS OF INTEREST

The authors declare that they do not have any conflicts of interest regarding the content of this study and manuscript.

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