

Effects of Dietary Induced Weight Loss on Exercise-Induced Bronchoconstriction in Overweight and Obese Children

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Summary. Rationale: Previous studies showed that obesity in asthmatic children is associated with more severe exercise-induced bronchoconstriction (EIB), compared with non-obese asthmatic children. This study investigates the effect of weight loss on EIB in overweight and obese asthmatic children. Methods: In this intervention study, children aged 8–18 years with EIB and moderate to severe overweight, followed a diet based on healthy daily intake for 6 weeks. Before and after the diet period they underwent an exercise challenge test in cold air. Primary outcome was change in exercise-induced fall in FEV₁ and relation between weight loss and EIB. Secondary outcomes were changes in recovery of FEV₁ ("area under the curve"; AUC), fraction of exhaled nitric oxide (FeNO) and scores of the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) and Asthma Control Questionnaire (ACQ). Results: Twenty children completed the study. After the diet period, weight, and body mass index (BMI) were significantly reduced (changes respectively –2.6% and –1.5 kg/m², $P < 0.01$). There was a significant improvement of the percentage exercise-induced fall in FEV₁ (30.6% vs. 21.8%, $P < 0.01$), AUC and PAQLQ score. The reduction in BMI z-score was significantly related to the reduction in the percentage exercise-induced fall in FEV₁ in children that lost weight ($r = 0.53$, $P = 0.03$). There were no changes in FeNO and ACQ. Conclusions: Dietary induced weight loss in overweight and obese asthmatic children leads to significant reduction in severity of EIB and improvement of the quality of life. The reduction in BMI z-score is significantly related to the improvement of EIB. **Pediatr Pulmonol.** © 2013 Wiley Periodicals, Inc.

Key words: asthma; diet; exercise-induced asthma; obesity.

Funding source: Pediatric Research Foundation Enschede

INTRODUCTION

Epidemiological studies in both children and adults show an important association between asthma and obesity.^{1,2} A recent study in 5–17 year old children with physician diagnosed asthma found that more than one-third were overweight or obese,^{3,4} and another study showed that the prevalence of asthma was significantly greater in obese children compared to non-obese children.^{3,5} So obesity seems to be a predisposing factor for the development of asthma and compromises asthma

control, through mechanisms that have not been completely elucidated yet.^{6,7}

Exercise-induced bronchoconstriction (EIB) is defined as a transient airway obstruction following exercise and measured as a fall in the forced expiratory volume in 1 sec (FEV₁) post-exercise.⁸ EIB is highly specific for asthma in children, reflects airway inflammation, and can be regarded as a sign of uncontrolled asthma.^{9–11} Obese asthmatic children have a greater exercise-induced fall in FEV₁ and a slower recovery from EIB than non-obese

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Conflict of interest: None.

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Received 17 December 2012; Accepted 17 August 2013.

DOI 10.1002/ppul.22932

Published online in Wiley Online Library (wileyonlinelibrary.com).

asthmatic children,^{12,13} which can limit their participation in physical and sporting activities with peers.

Several prospective studies in adults showed an association between weight loss and improvement of asthma outcomes, suggesting that obesity is not merely a consequence of asthma.² The effect of weight loss on EIB was studied in obese non-asthmatic adolescents by da Silva et al.,¹⁴ who showed an improvement of EIB occurrence after weight loss. The effect of weight loss in obese asthmatic children is unknown, and a recent review emphasized the need for weight loss trials in overweight asthmatic children.¹ The aim of this study is to investigate the effect of dietary induced weight loss on EIB in children with asthma and moderate to severe overweight. We hypothesize that weight loss in overweight and obese asthmatic children can improve severity of EIB.

MATERIALS AND METHODS

Study Design

This intervention study had a prospective open-label design and was performed between December 2010 and April 2011. Included children were instructed to follow a written diet for 6 weeks. Before and after the diet period they underwent an exercise challenge test, measurement of fractional concentration of exhaled nitric oxide (FeNO) and filled out the Asthma Control Questionnaire (ACQ) and Pediatric Asthma Quality of Life Questionnaire (PAQLQ). Weight (kg), height (m), BMI (kg/m^2), and BMI z-score (SD from the age- and gender-adjusted mean^{15–17}) were determined before and after the diet period. The study protocol was approved by the local Medical Ethics Committee and was registered in the Dutch Trial register (NTR2631). All children and their parents received written patient information and signed an informed consent form before study entry.

Subjects

We recruited children, aged 8–18 years, with pediatrician diagnosed asthma and overweight or obesity, from the outpatient clinic of the pediatric department of Medisch Spectrum Twente, Enschede. Overweight and obesity were defined as a BMI $\geq$ the age- and gender-related cut off points, linked to the widely accepted adult cut off points of overweight (BMI $\geq 25 \text{ kg}/\text{m}^2$) and obesity (BMI $\geq 30 \text{ kg}/\text{m}^2$).^{16,17} Other inclusion criteria were the presence of EIB, defined as a $\geq 10\%$ exercise-induced fall in FEV₁ at a screening exercise challenge, and clinical stable asthma (i.e., baseline FEV₁ $> 70\%$ of predicted normal value and no hospital admission or use of systemic corticosteroids 3 weeks prior to study entry). Exclusion criteria were pulmonary or cardiac co-morbidity, and use of systemic corticosteroids during the study. No short- and long-acting bronchodilators were used, respectively 8 and

24 hr before testing. Daily physical activities and medication regimen did not change during the study.

Diet

Included children and their parents received written information about the diet at study entry. The children were instructed to follow a nutritional chart (different for the ages 8–10, 11–14, and 15–18 years) based on a healthy daily intake, approved by a certified dietician. Children and parents were encouraged to have three meals a day, normalise portion sizes and minimize eating snacks (maximum two times daily). During the diet period, children visited the hospital twice. We contacted them weekly by telephone in order to motivate them, thus improving adherence to the diet.

Spirometry

Spirometry was performed before (baseline) and after exercise, using a standardized protocol according to international guidelines.¹⁸ We used a MicroLoop spirometer with impeller, in combination with Spida5 software, to measure flow volume curves. Calibration of the spirometer was weekly checked. The expiratory flow volume curve was recorded by instructing the children to perform a maximal expiratory effort from inspiratory vital capacity to residual volume. All measurements were performed in duplex, pulmonary function was calculated from the best curve according to ATS/ERS criteria.¹⁸

Exercise Challenge Test

Exercise challenge testing was performed by running on a treadmill (Horizon fitness Ti22), wearing a noseclip, using a standardized protocol.¹⁹ The exercise tests were performed in the local skating rink at the IJssbaan Twente, Enschede, in order to obtain cold, dry air with a temperature of 9.5–10.0°C and humidity of 57–59% (5.5–6.0 mg H₂O/L). During the test, heart rate was continuously monitored by means of radio telemetry (Sigma Sport PC3). The test started with running at low speed on the treadmill with an incline of 10%. During the first 2 min the running speed was increased, raising the heart rate to approximately 85% of the predicted maximum $((220 - \text{age}) \times 0.85)$.¹⁹ This speed was maintained for a total of 6 min. After exercise, flow volumes were measured at 1, 3, 6, 9, 12, 15, 20, 25, and 30 min. Thirty minutes after exercise, or at request, patients received 100 μg salbutamol, after which a flow volume curve was repeated. The maximum percentage fall in FEV₁ compared to baseline was used for further analysis. AUC was calculated by multiplying the mean fall in FEV₁ between two measurements with duration of the interval (in minutes). Total AUC is the sum of all values between 0 and 30 min post-exercise.

Questionnaires

The ACQ is a validated questionnaire to measure asthma control.²⁰ Responses are given on a seven-point scale and the overall score is the mean of the responses. A mean score <0.75 is considered as well-controlled asthma, a score >1.50 as inadequately controlled asthma.²⁰ The PAQLQ has three domains: symptoms, activity limitations, and emotional function. The mean item score is reported per domain and for the whole instrument, ranging from 1 (impaired quality of life) to 7 (no impairment in quality of life). A 0.5 point change in mean score is considered as clinically relevant.^{21,22}

Exhaled Nitric Oxide

Single FeNO measurements were performed, according to current guidelines, using the NIOX MINO.²³ Children inhaled to total lung capacity and immediately exhaled at a constant flow rate of 50 ml/sec. A poor asthma control is defined as FeNO levels exceed 30 parts per billion (ppb).²⁴ Levels below 20 ppb are indicators of good asthma control.²⁴

Statistical Analysis

Results were expressed as mean values $\pm$ standard deviation (SD) for normally distributed data, as median (minimum;maximum) for not normally distributed data or as numbers with corresponding percentages if nominal or ordinal. Body mass index (BMI) was adjusted for age and gender and calculated as SD from the mean (BMI z-score), according to the Fourth Dutch Growth Study.^{15–17} Continuous variables were tested for normality with a Shapiro–Wilk test. Changes in characteristics after the diet period were determined by using a paired samples *t*-test (if normally distributed) or Wilcoxon-signed rank sum test (if not normally distributed). Correlation between BMI z-score and EIB was calculated using a Spearman correlation. A two-sided value of $P < 0.05$ was considered statistically significant. All analyses were performed with the Statistical Package for the Social Sciences (SPSS) for Windows version 15 (IBM, Chicago, IL).

Before inclusion, sample size calculation was performed. A calculated sample size of 29 subjects would achieve 80% power to detect a correlation of 0.5 between the change in BMI and the change in the exercise-induced fall in FEV₁ using a two-sided hypothesis test with a significance level of 0.05.

RESULTS

Patient Characteristics

Thirty-three patients were screened for inclusion in the study. Twelve children were excluded because they had a $<10\%$ exercise-induced fall in FEV₁ and one child was

excluded, because of a baseline FEV₁ of $<70\%$ predicted value. Of the 20 included children (15 male), 13 were overweight and 7 were obese, according to the age- and gender-related cut off points linked to adult cut off points of overweight (BMI ≥ 25 kg/m²) and obesity (BMI ≥ 30 kg/m²).^{16,17} Mean age was 11.6 ± 2.5 years. The medication use is shown in Table 1.

Weight Reduction

After the diet period of 6 ± 0.5 weeks (slight variation due to logistics), weight, BMI, and BMI z-score were significantly reduced, as can be seen in Table 2 and Figure 1A. The mean loss of pretreatment weight was $2.6 \pm 2.9\%$, $P < 0.01$. Three children did not attain our intervention goal of losing weight. There was no difference in weight reduction between obese and overweight children (data not shown).

Exercise-Induced Bronchoconstriction

The maximum exercise-induced fall in FEV₁ was significantly reduced after the diet period, as can be seen in Figure 1B and Table 2. Children had a quicker recovery of FEV₁, measured as reduction in total AUC, after the diet period. There was a significant, moderate correlation between the reduction in BMI z-score and the reduction in the percentage exercise-induced fall in FEV₁ in the 17 children that lost weight ($r = 0.53$, $P = 0.03$), Figure 2. Two of the three children that did not lose weight had a reduced maximum exercise-induced fall in FEV₁ after the diet period, one child had an unchanged maximum fall in FEV₁.

The intensity of both exercise tests was individually titrated with heart rate. Retrospective analysis showed that mean running speed was similar before and after the diet period (6.1 ± 0.6 km/hr, $P = 0.89$). Mean heart rate (as percentage of maximum) during exercise was lower after the diet period (86.7 ± 4.5 versus 83.4 ± 4.7 , $P < 0.01$).

Secondary Outcomes

Median overall PAQLQ score and median PAQLQ score in symptoms and activity limitations domains significantly improved after the diet period, of which the

TABLE 1—Medication Use (N = 20)

Medication	Number (%)
SABA	20 (100)
LABA	3 (15)
ICS	18 (90)
AH	4 (20)
NCS	11 (55)

SABA, short-acting β_2 -agonist; ICS, inhaled corticosteroids (beclomethasone 100–400 μ g daily or fluticasone 125–250 μ g daily); LABA, long-acting β_2 -agonist; AH, antihistamine; NCS, nasal corticosteroids. Results expressed as numbers (percentages).

TABLE 2—Characteristics Before and After the Diet Period

Characteristics	Before diet	After diet	P-value
Weight (kg)	58.6 (41.2;98.4)	56.8 (40.6;98.3)	<0.01
BMI (kg/m ²)	25.7 (20.9;31.5)	24.2 (20.6;31.5)	<0.01
BMI z-score (SD from adjusted mean)	2.2 ± 0.4	2.0 ± 0.5	<0.01
Maximum exercise induced fall in FEV ₁ (%)	30.6 (9.5;67.3)	21.8 (6.6;65.2)	<0.01
AUC for FEV ₁ (time (min) % fall in FEV ₁)	588 (119;1404)	317 (30;1018)	0.01
Baseline FEV ₁ (l)	2.49 ± 0.72	2.51 ± 0.76	0.66
Baseline FEV ₁ (% predicted)	92.1 ± 12.7	91.9 ± 11.4	0.93
FVC (% predicted)	97.5 ± 11.1	99.2 ± 11.0	0.25
Tiffeneau index (FEV ₁ /FVC·100)	79.5 ± 9.7	78.3 ± 7.4	0.39
FeNO (ppb)	31.5 ± 17.3	31.9 ± 20.4	0.93
ACQ (mean score)	1.1 (0.1;2.9)	0.7 (0.0;2.9)	0.16
PAQLQ (mean score)	6.2 (3.4;6.8)	6.5 (3.7;7.0)	<0.01
Symptoms	5.9 (3.4;7.0)	6.6 (3.9;7.0)	0.01
Activity limitations	5.8 (3.4;7.0)	6.2 (3.2;7.0)	0.02
Emotional function	6.8 (3.3;7.0)	6.9 (3.0;7.0)	0.08

BMI, body mass index; FEV₁, forced expiratory volume in 1 sec; AUC, area under the curve for forced expiratory volume in 1 sec; FVC, forced vital capacity; FeNO, fraction exhaled nitric oxide; ppb, parts per billion; ACQ, asthma control questionnaire; PAQLQ, pediatric asthma quality of life questionnaire.

Results expressed as median (minimum;maximum) or as mean values ± SD.

change in the symptoms domain was clinically significant. ACQ score and FeNO did not significantly change after the diet (Table 2).

DISCUSSION

The main finding of this study was that even a small reduction of BMI following a diet based on healthy daily

intake can improve severity of EIB in overweight and obese asthmatic children. The reduction in BMI z-score was related to the improvement of the percentage exercise-induced fall in FEV₁.

To our knowledge, the effect of weight loss on EIB in overweight and obese asthmatic children has not been investigated before. The effect of weight loss on EIB was

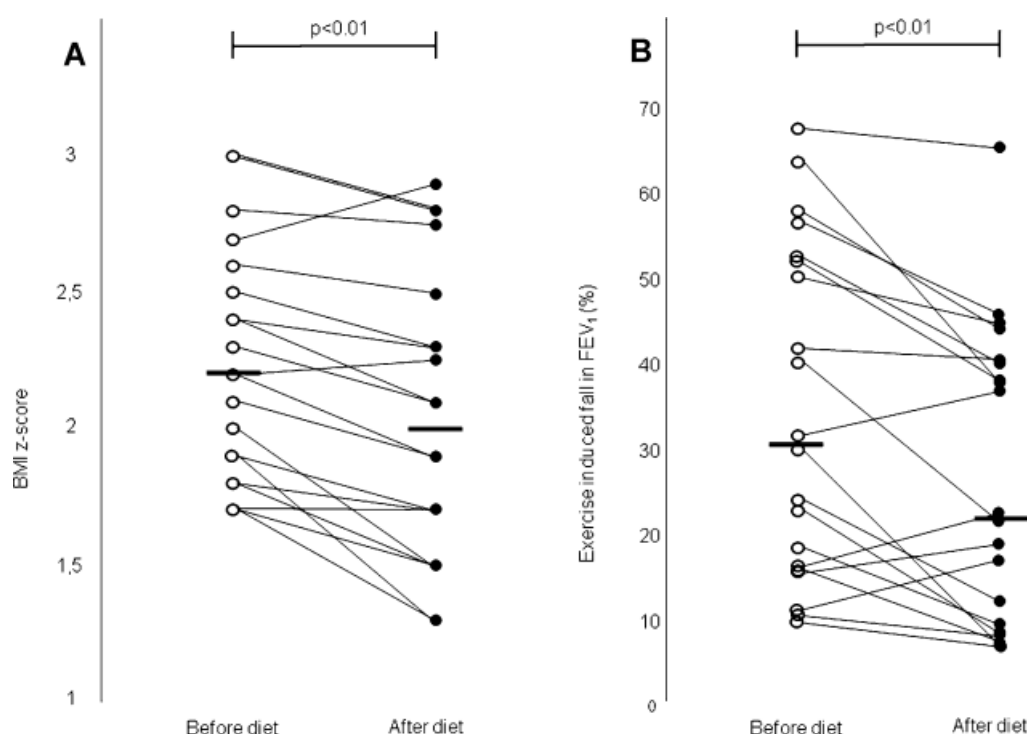


Fig. 1. Changes in BMI z-score (A) and exercise-induced fall in FEV₁ (B) after the diet period. As individual changes (circles) and means or medians (lines). BMI, body mass index (kg/m²); FEV₁, forced expiratory volume in 1 sec; ○, before diet; ●, after diet.

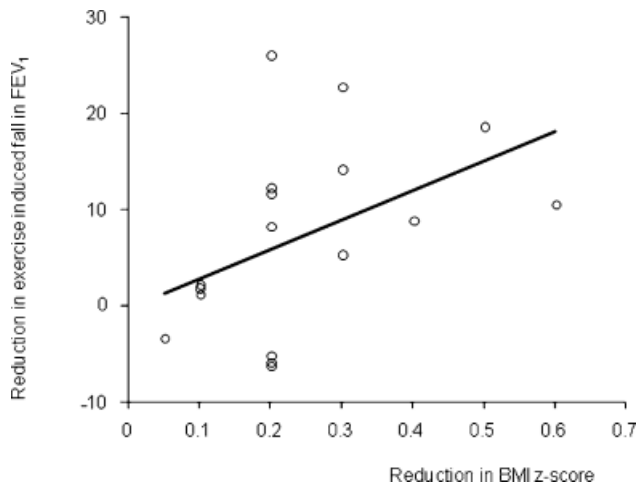


Fig. 2. Relation between reduction in BMI z-score and reduction in percentage exercise induced fall in FEV₁ (absolute change in maximum % fall). FEV₁, forced expiratory volume in 1 second; BMI, body mass index (kg/m²).

investigated in one study, performed in 35 obese non-asthmatic adolescents, aged 15–19 years old, of which 15 had EIB.¹⁴ After a 1-year interdisciplinary weight loss therapy, consisting of exercise training and medical, nutritional, and psychological therapy, there was a reduction of EIB prevalence to 0%.¹⁴ Although the positive effect of weight loss on EIB as described by da Silva et al.¹⁴ is in line with our findings, their results cannot be extrapolated to asthmatic children, as the pathophysiology of EIB in non-asthmatic obese patients is probably different.¹ In obese adults, several studies have investigated the effect of weight loss on asthma outcomes.² Regardless of the mode of intervention (bariatric surgery or diet), all studies found an improvement in at least one asthma outcome, such as use of asthma medication, severity of asthma symptoms or resolution of asthma symptoms.²

Besides reduction in the severity of EIB, our results also showed a clinically significant improvement in quality of life with regard to asthma symptoms, as measured by the PAQLQ symptoms score, after the diet period. This improvement could be due to both weight loss and reduction in the severity of EIB, as excessive body weight is associated with an additional decrease in quality of life in children with asthma.²⁵ Our study did not show a significant improvement in the ACQ score, which could be due to the small sample size or relatively short intervention period. There was no change in FeNO after the diet period, which may suggest a different mechanism for the influence of BMI on EIB.

Our study has some limitations. First, we did not include a control group of overweight asthmatic children that did not follow a diet. Simply participating in a study could conceivably improve subjective outcomes and adherence to medication, and thus severity of EIB.

However, we assumed that the improvement of EIB in our study was due to the weight loss, as we found a significant relation between reduction in BMI z-score and severity of EIB in children after losing weight. Moreover, a previous placebo controlled trial with a comparable design, performed by our own group, showed that there was no change in EIB in a control group.²⁶ We cannot exclude that dietary changes in itself, such as changes in types of food eaten, have affected EIB.

Secondly, our study was slightly underpowered since 13 of the recruited children were excluded. However, in spite of this, we did find a significant and relevant improvement in severity of EIB and quality of life. We individually titrated the intensity of both exercise tests with heart rate (with the aim of achieving approximately 85% of maximum heart rate). Mean heart rate during exercise appeared to be 3% lower after the diet period, which was statistically significant, but we considered it not to be of clinical relevance.¹⁹ Our study group consisted predominantly of male children (75%), which we considered to be the consequence of the difference in asthma prevalence in childhood (prevalence in boys is about 50% higher than in girls²⁷), rather than selection bias.

Several mechanisms have been suggested to explain the beneficial effect of weight loss on asthma outcomes. First, weight loss improves chest wall mechanics.^{1,2} In obese asthmatics, chest wall and abdominal adipose tissue cause dysfunctional chest wall mechanics and decrements in tidal volumes.^{2,28} These hinder deep inspirations and subsequent airway smooth muscle relaxation, which are necessary to prevent bronchoconstriction.^{2,29,30} The decreased smooth muscle stretch in obese asthmatics results in latching of smooth muscle, which leads to enhanced airway hyperresponsiveness and sustained airway obstruction.^{2,28} Second, weight loss might decrease systemic and airway inflammation.¹ Obesity is considered to be an inflammatory state with increased levels of hormones, such as leptin, and chemokines and cytokines, such as tumour necrosis factor and interleukins, which all can play a role in airway inflammation and the development of bronchial hyperresponsiveness.^{1,28,31} Several studies have suggested that relative body fat loss in obese children is associated with a reduction in systemic inflammation, explaining the positive effect on asthma outcomes.¹ The relation between obesity and asthma can also be explained by a more sedentary lifestyle in asthmatic patients, leading to obesity. However, this theory is not compatible with the positive effects of weight loss on asthma outcomes, observed in several studies.² Moreover, evidence from prospective studies in adults and children suggested that obesity precedes asthma and that weight gain is associated with an increased risk of asthma.^{1,7,32}

In conclusion, our study showed that a relatively small reduction of BMI through a diet based on healthy daily intake, improves severity of EIB in overweight and obese asthmatic children. This indicates the potential importance of dietary intervention and weight management in the clinical management of the overweight child with asthma. Moreover, dietary induced weight loss is associated with improved quality of life, which is valuable to patients with low self-esteem as a result of overweight and EIB. The results of our study provide pilot data to support the design of larger randomized controlled trials investigating the short and long-term effect of dietary induced weight loss on EIB in asthmatic children.

ACKNOWLEDGMENTS

The authors would like to thank IJsbaan Twente, Enschede, and its employees for their assistance, Elin Kersten for her help in conceptualizing the study and Jean Driessen and Reina Visser for their help in data collection.

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