Overweight and exercise-induced bronchoconstriction – is there a link?

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Tutkielma

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TIIVISTELMÄ

Tämän tutkimuksen tarkoitus oli arvioida painoindeksin yhteyttä fyysiseen suorituskykyyn, rasitusastmareaktioon ja rasituksen laukaisemiin hengitystieoireisiin (yskään, vinkunaan ja hengenahdistukseen) kouluikäisillä lapsilla.

1120 ulkojuoksukokeen tulokset käytiin retrospektiivisesti läpi. Nämä ulkojuoksukokeet oli suoritettu Iho- ja allergiasairaalassa osana kouluikäisten lasten tavanomaisia astmaselvittelyjä. Keuhkojen toimintaa arvioitiin spirometrialla. Astmalle diagnostisen rasituksen laukaiseman keuhkoputkien supistumisen eli rasitusastmareaktion rajana pidettiin vähintään 15 prosentin laskua uloshengityksen sekuntikapasiteetissa rasituksen jälkeen. Fyysinen suorituskyky arvioitiin laskemalla todellisesta juoksuajasta ja -matkasta 6 minuutissa juostu matka. Hengitystieoireet ja -löydökset kirjattiin kokeen aikana, ja lasten ikään ja sukupuoleen suhteutettu painoindeksi eli ISO-BMI laskettiin kansallisia kasvuviitearvoja käyttäen.

Suurempi ISO-BMI ja ylipaino ennustivat heikompaa fyysistä suorituskykyä. Lisäksi suurempi ISO-BMI oli yhteydessä yskään ja hengenahdistukseen rasituskokeen aikana. Sen sijaan ISO-BMI ei liittynyt rasitusastmareaktioon eikä vinkunaan.

Tämän tutkimuksen löydösten perusteella kouluikäisillä lapsilla ylipaino voi ennustaa heikompaa fyysistä suorituskykyä ja rasitusperäisten hengitystieoireiden ilmaantumista, mutta ei rasitusastmareaktiota. Mikäli asianmukaisia keuhkojen toimintatutkimuksia ei suoriteta, voidaan astmadiagnoosi asettaa väärin perustein. Tutkimus on toistaiseksi suurin kouluikäisten lasten ylipainon, rasitusastmareaktion ja fyysisen suorituskyvyn yhteyttä tarkasteleva tutkimus, mutta koska tutkimus oli luonteeltaan retrospektiivinen asiakirjatutkimus, tulokset tulisi jatkossa vahvistaa prospektiivisella seurantatutkimuksella.

AVAINSANAT

BMI, exercise-induced bronchoconstriction, wheeze, shortness of breath, cough, physical fitness, asthma, pediatrics

INTRODUCTION

The association between asthma, poor physical fitness, and overweight has been investigated in various studies in adults, but among school children the issue has been evaluated inconclusively.[1] Overweight is supposed to increase the risk of asthma,[2-4] but the findings on its effects on bronchial hyperresponsiveness have been incoherent.[5-7] Overweight has also been associated with poor physical fitness,[1,8] which can be one of the reasons for exercise-induced respiratory symptoms eliciting asthma investigations. Exercise-induced cough, wheeze, and shortness of breath are often interpreted as signs of asthma, but the correlation between the symptoms and actual bronchial hyperresponsiveness has proven to be poor.[9-10]

Children with asthma may also suffer from impaired physical fitness.[11] Regular exercise seems to be positively associated with milder bronchial hyperresponsiveness in asthmatic children,[12] but it is not clear whether this is due to good cardiorespiratory fitness or other benefits of exercise.

The main goal of this study was to evaluate the role of body mass index (BMI) with regard to physical performance, respiratory symptoms, and bronchial hyperresponsiveness, as expressed by exercise-induced bronchoconstriction (EIB), in a large sample of children with respiratory symptoms suggestive of asthma.

METHODS

Study material

The original study material included documented outdoor free-running test results for 1120 children (aged 7-16 years) with spirometry performed in a tertiary hospital in 2014-2015. As the free-running test was included as a part of routine asthma investigations, no separate visits or examinations were required from patients for this study. Children were classified as having asthma, if they presented with a typical symptom history, and showed evidence of variable airflow obstruction or bronchial hyperresponsiveness,[13] by using the following tests: spirometry with a bronchodilator test, an outdoor running test, a provocation test with histamine or methacholine and/or a 2-week peak expiratory flow (PEF) surveillance. Patients with no recordings of running time or distance, or those with uncertain asthma diagnosis (n=100) were excluded from the analyses. Severe heart disease or chronic disease other than asthma that might exacerbate during exercise was considered as a contraindication for an outdoor running test.

Ethics

The study was conducted according to the principles of the Declaration of Helsinki. As the study was a retrospective review of medical records and exercise challenge measurements, according to institutional principles, permission for the study was requested from the institutional board, but no review from ethics committee was considered to be needed.

Outdoor free-running test

The exercise test was performed on a running track near the tertiary hospital. The test consisted of outdoor running on the signed track for 6-8 minutes, while heart rate was monitored (Vantage NV, Polar Ltd, Kempele, Finland) and respiratory rate recorded. Running distance was measured and recorded along with the running time. Possible respiratory symptoms were observed by the physician overseeing the test and/or reported by the patient. Lung function was evaluated with spirometry according to standard principles,[14-15] with a pneumotachograph-based flow-volume spirometer (Masterscreen Pneumo, Carefusion, Hoechberg, Germany). The following parameters were recorded: forced expiratory volume in 1 second (FEV1), forced vital capacity

(FVC), and FEV1/FVC ratio. Spirometric raw values were transformed into z-scores based on national reference values.[16] Z-score values of ≤ -1.65 standard deviation (SD) were considered as abnormal.

During the running test, spirometric measurements were repeated before the exercise, and immediately, 5 minutes, and 10 minutes after the exercise. After this, inhaled salbutamol was administered, and the final spirometric measurements were performed. A fall of 15% or more in FEV1 after the exercise was considered indicative of significant EIB.

Physical performance

Physical performance was measured by calculating the running speed and distance per 6 minutes from the running time and distance in the outdoor free-running test. To ensure that patients would give their maximal physical performance, they were urged to reach at least 85% of their predicted maximum heart rate (calculated with the formula 208 - (0.7 x age).[17]

BMI

As BMI (i.e., weight divided by square of height) is not well suited for evaluating children's body composition, we used ISO-BMI, i.e. BMI modified for children. ISO-BMI gives values that are better comparable to those of adults; for example, ISO-BMI ≥ 25 is considered as overweight. ISO-BMI was calculated for each child from height, weight, age, and gender according to the national growth references.[18]

Statistical analysis

Normality of the continuous variables was evaluated using Kolmogorov-Smirnov's test. The effects of continuous baseline variables on a maximal fall in FEV1 and on a running distance per 6 minutes were evaluated using Pearson's correlation test, and on categorical variables using T-test. Linear regression analysis was used for determining variables independently associated with a maximal fall in FEV1 and physical performance. Logistic regression analysis was used for determining variables independently associated with exercise-induced respiratory symptoms and EIB. Variables for the multivariate models were chosen with the backward selection method. P-value of <0.05 was considered statistically significant. IBM SPSS Statistics Version 22 was used for statistical analyses.

RESULTS

Baseline characteristics

Baseline characteristics of the study children are presented in Table 1.

555 children were diagnosed as having asthma. 189 children had EIB in the outdoor running test. 212 children were overweight, and their age and gender distribution were similar to children with normal weight. There were no statistically significant differences in ISO-BMI ($p=0.264$) or being overweight ($p=0.136$) between the children with and those without asthma.

Physical performance

Correlations to physical performance are presented in Table 2. Greater ISO-BMI and overweight (Fig. 1) were associated with poorer physical performance. Higher outdoor temperature and age were associated with better physical performance. Males ran faster than females ($p<0.001$), and those with any respiratory symptoms (cough ($p<0.001$), wheeze ($p<0.001$), or shortness of breath ($p=0.003$)) during the exercise challenge test ran slower than those without respiratory symptoms.

In the linear regression analysis including the entire study group, variables independently associated with poorer physical performance were younger age ($p<0.001$), female gender ($p<0.001$), greater ISO-BMI ($p<0.001$), lower outdoor temperature ($p<0.001$), lower FEV1 z-score ($p=0.008$), and appearance of any respiratory symptoms during the exercise challenge test ($p=0.023$). The adjusted R square for this model was 0.321.

In the linear regression analysis including only the non-asthmatic children, age, weight, height, and gender were the variables independently associated with physical performance. This gave us the following regression model equation for predicting physical performance (distance per 6 minutes) in non-asthmatic children: y = A + B x age + C x height + D x weight + E x gender (A=-127.375, B=21.488, C=6.993, D=-6.733, E=67.185, male=1, female=0). The adjusted R square for this model was 0.414.

EIB

Correlation analyses with a maximal change in FEV1 are presented in Table 3. Younger age, lower outdoor temperature, poorer physical performance, and a lower pre-exercise

FEV1/FVC z-score were associated with a greater fall in FEV1. Neither pre-exercise FEV1 z-score nor ISO-BMI had statistically significant association with a maximal change in FEV1.

EIB was associated with abnormal FEV1/FVC z-score ($p<0.001$) and any respiratory symptoms ($p<0.001$) during the exercise challenge test. Younger age ($p<0.001$), lower outdoor temperature ($p<0.001$), and poorer physical performance ($p<0.001$) were also associated with EIB.

In the logistic regression analysis, variables independently associated with EIB were younger age ($p<0.001$), lower outdoor temperature ($p=0.026$), FEV1/FVC z-score ≤ -1.65 ($p=0.011$), and any respiratory symptoms during the exercise challenge test ($p<0.001$). The adjusted R square for the model was 0.317.

Exercise-induced respiratory symptoms

572 children were symptomless, 219 had cough, 140 had wheeze, and 299 experienced shortness of breath during or after the exercise challenge. 50 children had both cough and shortness of breath, 15 had cough and wheeze, 69 had wheeze and shortness of breath, and 38 experienced all three symptoms.

In the univariate analysis, EIB ($p<0.001$), greater ISO-BMI ($p<0.001$ for cough, $p=0.041$ for wheeze, $p=0.002$ for shortness of breath), slower running speed ($p<0.001$ for cough and wheeze, $p=0.002$ for shortness of breath), lower outdoor temperature ($p<0.001$), lower FEV1/FVC z-score ($p=0.05$ for cough, $p<0.001$ for wheeze, $p=0.003$ for shortness of breath), and a greater fall in FEV1 ($p<0.001$) were all associated with an increased risk for cough, wheeze, and shortness of breath. Lower FEV1 z-score was associated with a greater risk for wheeze ($p=0.039$) and shortness of breath ($p=0.017$), but not for cough.

Multivariate models for predicting exercise-induced respiratory symptoms in the entire study population are presented in Table 4. Variables independently associated with cough were greater ISO-BMI, lower outdoor temperature, and EIB. Variables independently associated with shortness of breath were older age, greater ISO-BMI, lower outdoor temperature, and EIB. Variables independently associated with wheeze were lower outdoor temperature and EIB.

DISCUSSION

To our knowledge, this study is the largest that has investigated the interrelationships of overweight, physical performance, and EIB in children with respiratory symptoms suggestive of asthma. A greater ISO-BMI was associated with poorer physical performance and appearance of cough and shortness of breath during the exercise, but not with EIB or wheeze induced by the exercise. We found also a significant association between lower outdoor temperature and EIB.

Our study shows a correlation between greater ISO-BMI and poorer physical performance in the oudoor free-running test. This result is easily rationalized, as physical inactivity can cause both increase in weight and decrease in physical fitness. Ferreira et al. found that obese subjects walked shorter distances during a 6-minute walk test.[1] Obese children also performed poorly on a treadmill challenge compared to lean children.[9] Özgen et al. even found BMI standard deviation score to be the only independent factor influencing physical performance in a 6-minute indoor walk test,[8] whereas in our study with a larger sample, also age, gender, outdoor temperature, and FEV1 z-score were found as independent factors associated with physical performance, in addition to ISO-BMI.

Obesity and overweight have been associated with EIB in some studies.[6,8] The connection is suggested to be due to inflammatory mechanisms involving both conditions.[19] Experimental evidence shows that changes in lung mechanics in obesity may predispose to bronchial hyperresponsiveness.[20] In our study, ISO-BMI was not associated with EIB. Equal findings have been observed by others as well.[7] However, in most longitudinal studies, asthma and BMI have been associated, and the opposing results have only come from cross-sectional studies.[4] Obesity has been found to increase the risk of developing asthma in children,[2] but from epidemiological studies it is difficult to conclude whether clinical assessments leading to diagnosis of asthma have been biased by the increased amounts of respiratory symptoms due to obesity per se, and what has been the role of lung function measurements.

In our study, poor physical performance was correlated with a maximal fall in FEV1. Similarly, poorer physical fitness in childhood has been found to increase the risk of hyperresponsiveness to methacholine and the risk of developing asthma.[11-12] However, it is not clear whether poor physical fitness contributes to the development of asthma and bronchial hyperresponsiveness or whether poor physical fitness is caused by exercise avoidance due to the unpleasant exercise-induced respiratory symptoms in asthmatic children.

As expected, EIB had an independent association with all three symptoms. However, exercise-induced cough, wheeze, and shortness of breath have been found to be poor predictors for a diagnostic fall in FEV1.[9-10] Our observations support the concept that the symptoms are not specific for EIB, but also affected by ISO-BMI and outdoor temperature.

Even though physical performance was found to have an association with all the exercise-induced respiratory symptoms in the univariate analysis, it was not independently associated with the symptoms in the multivariate regression analysis. In contrast, ISO-BMI was an independent factor associated with both cough and shortness of breath; for wheeze, this association was not evident. Overweight predisposes to breathlessness by increasing metabolic demands for running and increasing breathing work.[21] Susceptibility for wheezing is higher in overweight subjects due to lower functional residual capacity (FRC) which increases airway resistance and promotes intrathoracic airway closure,[22] and due to extrathoracic airway obstruction caused by fat deposition.[23] Scholtens et al. concluded that dyspnea and wheeze were associated with a greater BMI in children aged 6 to 7 years.[24] On the other hand, there is evidence that lean subjects experience more dyspnea after exercise challenge compared to obese subjects.[8]

The outdoor free-running test has been found to mimic real-life EIB, and may give positive test results when other bronchial challenges do not.[25] The outdoor free-running test enables the evaluation of patient's physical fitness, as the running time and distance are recorded. Compared to i.e. treadmill test in the laboratory, the outdoor running test is more feasible to investigate larger samples of subjects such as in the current study, but the inherent weakness is that the outdoor conditions (temperature, humidity) cannot be standardized. In this study, outdoor temperature was an independent factor associated with all three symptoms in the analyses including the entire study population. Respiratory symptoms are common in cold temperatures,[26] especially in those with asthma.[27] It is thought that exercise-induced hyperpnea causes drying and cooling of airway surface liquid, which triggers respiratory symptoms and EIB via vagal reflex mechanisms and by mast cell degranulation.[28] Shortness of breath during the exercise has been found to be more common in cold temperature than in normal room temperature, or simply during exposure to cold air.[29] Accordingly in our series, lower outdoor temperature was not only associated with exercise-induced respiratory symptoms, but also with a greater maximal fall in FEV1 and EIB. Similar results have also been reported in preschool children with asthma.[30]

Assessment of exercise-induced respiratory symptoms suggesting asthma in children is a common clinical problem. Considering the reliability of our results, this retrospective study has a reasonably good-sized cohort and well-documented data, as the running test was conducted in a standardized manner, including quantification of performance and high quality spirometric recordings. Even though the maximal performance was not measured, the running pace was adjusted to be symptom limited, and by monitoring the heart rate. One limitation is the lack of a proper control group. Children referred to exercise challenge test are always in some way symptomatic, and although those children in whom during careful assessment of symptoms and objective lung function tests asthma could not be confirmed, this group was biased and not necessarily composed of "healthy" individuals. Also, parental smoking was not considered in the exclusion criteria.

In conclusion, increase in weight was associated with exercise-induced cough and shortness of breath and poor physical performance, but not with wheeze or EIB. Respiratory symptoms in overweight children may be misinterpreted as asthmatic, unless objective lung function measurements are conducted. There was also a significant association between lower outdoor temperature and bronchial hyperresponsiveness. The conflicting findings in other studies call for more evidence on the matter, as well as better understanding on the underlying mechanisms linking obesity and asthma. Controlled intervention studies on the effects of improving physical performance in preventing and controlling of overweight and asthma in children should be done.

KEY MESSAGE

In this so far largest study of school aged children with asthmatic symptoms undergoing exercise challenge tests, we found no association between overweight and exercise-induced bronchoconstriction. However, overweight contributed significantly to exercise-induced respiratory symptoms as well as poor physical performance which may lead to misinterpretation in the clinical evaluation, unless the diagnosis is based on objective lung function measurements.

CONFLICT OF INTEREST

There is no conflict of interest concerning the authors of this manuscript. Study sponsors had no role in study design; the collection, analysis, and interpretation of data; the writing of the report; and the decision to submit the manuscript for publication.

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TABLES

Table 1. Baseline characteristics, lung function parameters, and physical performance in the study children.

Baseline characteristics	n=1020
Age, years	11.1 (2.6)
Males†	616 (60)
ISO-BMI, kg/m^2‡	22.1 (21.9; 22.4)
ISO-BMI ≥ 25 kg/m^2†	212 (21)
Lung function parameters	
Pre-exercise	
FVC, l‡	2.7 (2.6; 2.7)
FVC z-score, SD	-0.4 (1.2)
FVC z-score ≤ -1.65 SD†	138 (14)
FEV1, l‡	2.3 (2.2; 2.3)
FEV1 z-score, SD	-0.8 (1.1)
FEV1 z-score ≤ -1.65 SD†	228 (22)
FEV1/FVC, %	85.3 (6.6)
FEV1/FVC z-score, SD	-0.7 (1.1)
FEV1/FVC z-score ≤ -1.65 SD	201 (20)
Performance in exercise challenge	
Post-exercise	
Maximal FEV1 Δ, %§	-6.7 (-74.6; 17.9)
Maximal FEV1 Δ ≤ -15%†	189 (19)
Distance / 6 min, m	959.2 (141.2)

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ISO-BMI, body mass index modified for children according to national growth references; SD, standard deviation

The numbers presented denote mean (standard deviation), †n (%), ‡ geometric mean (95% confidence intervals), or § median (minimum; maximum).

Table 2. Correlations between physical performance and baseline characteristics including lung function in the study children.

	Distance / 6 min	
	r	p
Age	0.442	<0.001
ISO-BMI	-0.211	<0.001
Outdoor temperature	0.123	<0.001
Lung function parameters		
Pre-exercise		
FVC z-score	0.029	0.363
FEV1 z-score	0.038	0.231
FEV1/FVC z-score	0.004	0.888

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ISO-BMI, body mass index modified for children according to national growth references; p, probability value; r, correlation coefficient

Table 3. Correlations between bronchial hyperresponsiveness and baseline characteristics in the study children.

	Maximal fall in FEV1	
	r	p
Age	0.157	<0.001
ISO-BMI	-0.039	0.216
Outdoor temperature	0.135	<0.001
FEV1 z-score	0.061	0.053
FEV1/FVC z-score	0.141	<0.001
Distance / 6 min	0.161	<0.001

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ISO-BMI, body mass index modified for children according to national growth references; p, probability value; r, correlation coefficient

Table 4. Multivariate models for predicting symptoms in exercise challenge in the study children.

	Cough	Shortness of breath	Wheeze
Age	-	1.14 (1.06; 1.22)	-
ISO-BMI	1.08 (1.03; 1.13)	1.06 (1.01; 1.10)	-
Outdoor temperature	0.96 (0.94; 0.99)	0.96 (0.94; 0.99)	0.96 (0.92; 0.99)
EIB	8.95 (5.35; 14.99)	19.11 (11.60; 31.48)	48.97 (27.93; 85.87)
R^2 for the model	0.195	0.329	0.530

Abbreviations: EIB, exercise-induced bronchoconstriction; ISO-BMI, body mass index modified for children according to national growth references; R^2, coefficient of determination

The numbers presented denote odds ratio (95% confidence interval) or the proportion of the variance in the dependent variable that is predictable from the independent variables.

FIGURE

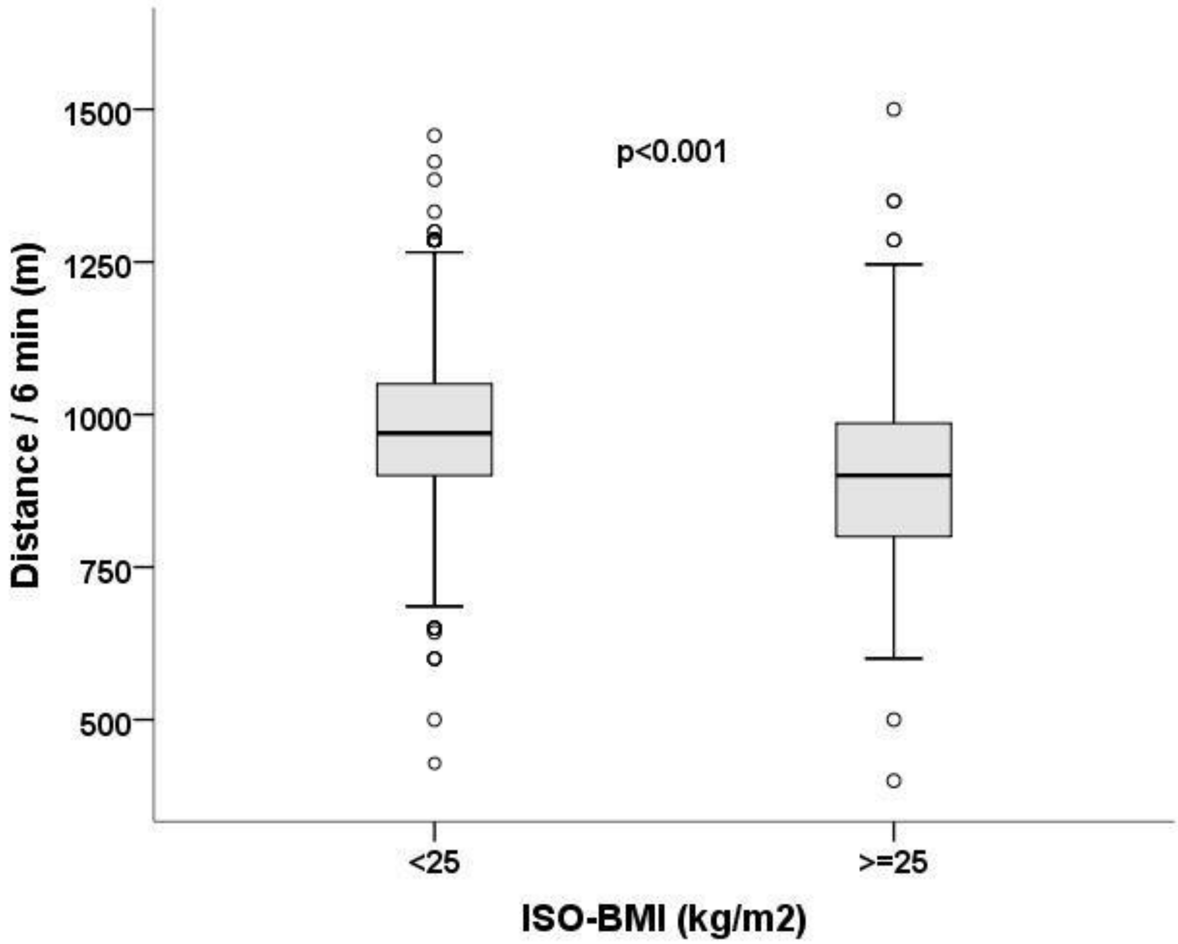

Figure 1. Physical performance (i.e. running distance in meters per 6 minutes) was better in children (n=808) with ISO-BMI < 25 kg/m^2 than in those (n=212) with ISO-BMI ≥ 25 kg/m^2.