Perceived exercise limitation in asthma: the role of disease severity, overweight and physical activity in children*

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Abstract

Background: Children with asthma may be less physically active than their healthy peers. We aimed to investigate if perceived exercise limitation (EL) was associated with lung function or bronchial hyperresponsiveness (BHR), socio-economic factors, prenatal smoking, overweight, allergic disease, asthma severity or physical activity (PA).

Methods: The 302 children with asthma from the 10-year examination of the Environment and Childhood Asthma birth cohort study underwent a clinical examination including perceived EL (structured interview of child and parent(s)), measure of overweight (body mass index by sex and age passing through 25kg/m^2 or above at18 years), exercise-induced bronchoconstriction (forced expiratory volume in one second (FEV_1) pre- and post-exercise), methacholine bronchial challenge (severe BHR; provocative dose causing ≥20% decrease in FEV1≤1µmol) and asthma severity score (dose of controller medication and exacerbations last 12 months). Multivariate logistic regression analyses were conducted to assess associations with perceived EL.

Results: In the final model explaining 30.1%, asthma severity score (OR 1.49, (1.32, 1.67)) and overweight (OR 2.35 (1.14, 4.82)) only were significantly associated with perceived EL. Excluding asthma severity and allergic disease, severe BHR (OR 2.82 (1.38, 5.76)) or maximal reduction in FEV_1 post exercise (OR 1.48 (1.10, 1.98)) and overweight (OR 2.15 (1.13, 4.08) and 2.53 (1.27, 5.03)) explained 9.7% and 8.4% of perceived EL, respectively.

Conclusions: Perceived EL in children with asthma was independently associated with asthma severity and overweight, the latter doubling the probability of perceived EL irrespectively of asthma severity, allergy status, socio-economic factors, prenatal smoking or PA.

Keywords (MeSH): Bronchial Hyperreactivity, Bronchial Provocation Tests, Cohort Studies, Exercise-Induced Asthma, Overweight, Pulmonary Function Tests, Self-Report, Socioeconomic Status

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Introduction

Asthma may result in reduced physical activity (PA) and thus poor physical fitness in childhood (1). Overweight children with asthma report greater limitations of PA (2). Improvement in asthma control by use of long-term controller medication is shown to be associated with increased PA (1). Furthermore, psychological adjustment to asthma and perceived competence of PA are positively associated with increased fitness in children with asthma (2, 3). Nevertheless, vigorous intensity PA may induce asthma symptoms in up to 90% of children with non-treated asthma and result in avoidance of PA (4).

The agreement between self-reported exercise-induced symptoms and objectively measured exercise-induced bronchoconstriction (EIB) is reported to be poor (5-7). Panditi and Silverman (7) found a weak association between children´s symptom perception and EIB, which was unaffected by age, gender, asthma severity, medication, habitual PA and attitudes towards PA or competitiveness. Seear et al. (5) and Joyner et al. (6) revealed that only 15% and 24% of children reporting exercise limitation met the criteria of EIB (decrease of ≥10% of forced expiratory volume in 1 second (FEV_1) post-exercise), respectively, explaining perceived exercise limitation (EL) by low cardiorespiratory fitness rather than EIB. Johansson et al. (8); however, reported a prevalence of EIB in 42% among adolescents reporting exercise induced dyspnea which was significantly higher compared with controls. Nevertheless, misinterpreted symptoms in symptom-based management may lead to further inactivity (5, 6), and differential diagnoses may be overlooked (5, 8, 9). Moreover, overprotection by parents, and children and parents´ misinterpretation of regular breathlessness during vigorous intensity PA may result in fear of asthma symptoms and restriction from participation in PA leading to further reduced fitness (10). Additionally, household stress factors related to low socioeconomic status are associated with perceived EL in children with asthma (11).

In the present study we aimed to investigate if perceived EL in children from a prospective birth cohort study with asthma was associated with reduced lung function or bronchial hyperresponsiveness (BHR), socio-economic factors, prenatal smoking, overweight, allergic rhinitis (AR), atopic eczema (AE), markers of asthma severity or by PA.

Materials and Methods

Study design and subjects

From the Environment and Childhood Asthma (ECA) birth cohort described elsewhere 1019 children attended the ten-year follow up (12). Children without suspicion of respiratory tract infection for the least 4 weeks, only, were included. Two clinical examinations with measures of BHR (EIB test and methacholine bronchial challenge on separate days) were performed 2–7 days apart after withholding short and long acting $ß_2$-agonists for at least 12 and 48 h, respectively, and leukotriene antagonists for 72 h. The present study comprises the 302 children (193 boys, 64%) with asthma out of the 1019 children examined at 10 years, who were similar to the remaining 717 children without asthma with respect to height, weight, household income, prenatal smoking, AR and AE.

Asthma (ever) was defined in accordance with previously reported criteria from ECA (12) by at least two of the following three criteria fulfilled: (i) Dyspnoea, chest tightness and/or wheezing 0-3 years and/or 4-10 years, (ii) a doctor´s diagnosis of asthma and (iii) used asthma medication (β_2-agonists, sodium chromoglycate, corticosteroids, leukotriene antagonists and/or aminophylline) 0-3 years and/or 4-10 years. *Allergic rhinitis* (ever) was defined with at least two out of three criteria fulfilled: (i) doctor's diagnosis of rhinitis, (ii) symptoms of rhinitis and (iii) treatment for eye/nose or allergy symptoms.

The study was approved by the Norwegian Data Inspectorate as well as the Regional Committee for Medical Research Ethics in South-Eastern Norway. Written informed consent to take part was obtained from guardians of the participating children.

Methods

Lung function was measured according to European standard (13) using SensorMedics Vmax 20c (SensorMedics Diagnostics, Yorba Linda, CA, USA), as forced expiratory flow volume loops reported as FEV_1, forced vital capacity (FVC), forced expiratory flow at 25-75% of FEV_1 (FEF_{25-75}) were presented as percent predicted according to Stanojevic et al. (14), in addition to FEV_1/FVC.

EIB tests were conducted as 6-8 minutes treadmill run with an exercise load of 95% of maximal heart rate during the last 4 minutes, following a standardized procedure (12, 15). The tests were considered positive as EIB with a reduction in FEV_1 ≥10% of baseline FEV_1 at three, six, ten, fifteen or twenty minutes after running ceased. Maximal reduction (%) in FEV_1 ($R_{Max}\%FEV_1$) post exercise compared with baseline was calculated.

Methacholine bronchial challenges with controlled tidal ventilation were performed according to American Thoracic Society (ATS) guidelines (16) by use of SPIRA® dosimeter (Spira Respiratory Care Center Ltd., Hemeenlinna, Finland). The starting dose was 0.05 µmol and the test continued until FEV_1 was reduced by 20% or a maximum cumulative dose of 22.4 µmol was reached. The tests were classified as positive in two categories with a provocative dose causing ≥20% decrease in FEV_1 (PD_{20}) of ≤8 µmol and ≤1 µmol respectively; the latter categorized as severe BHR.

Bronchodilator response was assessed by the highest value of FEV_1 after inhalation of Salbutamol 0.5 mg per 10 kg bodyweight 20 minutes post exercise. A bronchial lability index indicating of the total variability in FEV_1 (%) was calculated as the sum of the percentage decrease post exercise changes in FEV_1 plus the increase after Salbutamol inhalation compared to baseline (17).

Structured interview by a physician was conducted to collect data comprising respiratory symptoms of the child (ISAAC questions validated in Norwegian language (18)), use of medication, household income, parental education, prenatal smoking, PA and perceived EL. Daily PA was assessed by a positive answer of “PA accompanied with breathlessness and sweat 6-7 times each week”; hours participating in sports per week were assessed by “hours participating in organized exercise each week” and; perceived EL was assessed by a positive answer to the question: “present feeling that asthma restrains PA”. Self-reported daily PA and hours/week in sports were correlated with objectively recorded PA at 13 year measurements, described in detail elsewhere (19).

Anthropometric data were assessed measuring height with a stadiometer to nearest 0.5 cm and weight (Seca 709, Seca, Hamburg, Germany) to the nearest 0.1 kg wearing light clothing without shoes. Overweight was defined by international cut off points for body mass index by sex and age between 2 and 18 years according to Cole et al (20). Cut off points are designed to pass through $25kg/m^2$ at age 18 years.

An *asthma severity score* ranging from 0-9 was constructed based upon steps suggested by Taylor et al. (21). This score included the reported asthma controller medication (inhaled corticosteroids (ICS) and leukotriene antagonists and/or β_2-agonists) in addition to exacerbations reported during the last 12 months (classified as 0, 1-3, and >3). Description of the asthma severity score is given in table 1.

Statistical analysis

Chi-square tests were conducted to compare frequencies of categorical variables between children with and without asthma and between the groups with and without perceived EL. Continuous normally distributed variables are presented as mean with standard deviation (SD). Independent t-tests were used to analyze differences between groups. Skewed variables are presented as median with interquartile range (IQR), and Mann-Whitney Wilcoxon tests were preferred for calculating differences in not normally distributed data.

Variables with a significance level of ≤ 0.20 from bivariate analyses were considered for multivariate logistic regression analysis. Stepwise multivariate logistic regression analysis according to Hosmer et al. (22) was conducted, removing the least significant variable until only significant values remained. Results from logistic regression models are presented as Odds ratio (OR) with 95% confidence interval (CI).

Multivariate analysis was conducted in five separate models including one measure of BHR in each: EIB; $R_{Max}\%FEV_1$; $PD_{20} \leq 1$ μmol; $PD_{20} \leq 8$ μmol and; Bronchial lability index. To avoid multi-collinearity, each model included only one lung function variable with the lowest *p*-value (FEV_1/ FVC). Analysis of each model was repeated twice; first excluding asthma severity markers from the total models as severity was significantly associated with all five BHR variables. Secondly, allergic disease was additionally excluded from the reduced model due to significant associations with both PD_{20} variables and Bronchial lability index. All significant independent variables in each final model as well as gender were checked for interaction terms with perceived EL.

Statistical significance level was set to 5%. Nagelkerke R^2 was reported as explained variance from logistic regression models. Statistical analyses were performed with Statistical Package for Social Sciences Version 22.0 (SPSS, Chicago, IL, USA).

Results

Fifty eight (20%) children with asthma reported EL. As shown in table 2, these children had significantly larger $R_{Max}\%FEV_1$ post exercise as well as significantly more often severe BHR, more often a mother who smoked during pregnancy, overweight and comorbidity of both AR and AE than children without perceived EL. The asthma severity score was significantly higher and FEV_1/FVC lower in children with compared to without perceived EL. A non-significant (*p*=0.07) tendency to higher rate of positive EIB was found among children with (35%) compared to without (24%) perceived EL (Table 2). Groups did not differ significantly with regard to participation in sports or daily PA. Positive EIB-test, $PD_{20} \leq 1$, $PD_{20} \leq 8$ µmol, Bronchial lability index ≥10% or FEV1/FVC ≤80% individually or combined ranged from 29-67% in children with perceived EL.

In the final model, including gender, BHR, FEV_1/FVC, low household income, prenatal smoking, overweight, allergic disease, asthma severity score and hours/week in sports; asthma severity score (1.49 (1.32, 1.67)) and overweight (2.35 (1.14, 4.84)) only were independently associated with perceived EL (Fig. 1a). In the model 30.1% of the variance was explained. In the reduced model excluding asthma severity score 15.5% of the variance in EL was explained (Fig. 1b). Children more likely to report EL were those whose mother smoked during pregnancy (1.95 (1.02, 3.80)), overweight children (2.54 (1.30, 4.95)), children with AR only (3.03 (1.06, 8.69)), and children with comorbidity of AR and AE (5.53 (2.49, 12.31)).

BHR was significantly associated with perceived EL only when excluding both asthma severity score and allergic disease from analysis. Children with severe BHR were 2.82 (1.38, 5.76) times more likely (Fig. 2a), and children with 10 percent increased $R_{Max}\%FEV_1$

were 1.48 (1.10, 1.98) times more likely (Fig. 2b) to report EL, respectively. These models explained 9.7% and 8.4% of the variance in EL.

Overweight children were more than twice likely to report EL with significant associations to EL in all multivariate analysis (OR between 2.15 (1.13, 4.08) and 2.54 (1.30, 4.95)). This association was not significantly influenced by BHR, lung function, low household income, maternal prenatal smoking, allergic diseases, asthma severity score or hours per week in sports. Overweight did not significantly influence the associations between perceived EL and asthma severity score, comorbidity of AR and AE or BHR. There were no significant interactions between independent variables and perceived EL in the reported models.

Discussion

Exercise limitation was reported in 20% of children with asthma. In the final model explaining 30.1%, asthma severity score and overweight only were significantly associated with perceived EL. Excluding asthma severity and allergic disease, 9.7% and 8.4% of perceived EL were explained by significant associations to overweight and severe BHR or $R_{max}\%FEV_1$ post exercise, respectively. Overweight children were more than twice likely to report EL irrespectively of any other included factor.

The 20% of children reporting EL is lower than the general activity limitation reported in 52% of children with current asthma (23), although the frequency of EIB (35%) among children reporting EL in the present study was comparable to previously reported range between 8-42% in studies comparing self- reported symptoms with EIB test(5, 6, 8, 9, 24). Nevertheless, 67 out of 264 (25%) had a positive EIB compared to previously reported 51-55% (25, 26) including also children with current asthma and ICS treatment. The variations in rate of reported EL or exercise-induced symptoms and associations between EIB and perceived exercise-induced symptoms (5-8) may be related to study populations, asthma definitions and control. Children with asthma ever in the present birth cohort study are likely to have less severe asthma (27) than the current asthma patients in the study by Yeatts et al. (23). Also, different assessments may affect the rate of EL or EIB, with our children responding to a question whether they experienced that their asthma restricted their physical activity, compared to limited activities because of wheezing ≥1 times per month.

Despite no significant association between a positive EIB and perceived EL, the associations between $R_{max}\%FEV_1$ as well as severe BHR and EL suggest that perceived EL reflects BHR. This is supported by a report by Sanchez-Garcia et al. (24) suggesting that the direct methacholine challenge and the indirect mannitol tests have high sensitivities to detect

BHR in steroid naive children complaining of one or more symptoms after exercise. Sanchez-Garcia et al. (24) reported a detection rate of BHR in 96.7% with a methacholine test, increasing to 100% when combined with mannitol test (24). In contrast, Anderson et al. (28) reported a sensitivity of 59% and 56%, and a specificity of 65% and 69% to identify objectively measured EIB by mannitol and methacholine, respectively (28). The American Thoracic Society guidelines recommend mannitol test or hyperosmolar aerosols of 4.5% saline or eucapnic voluntary hyperpnoea of dry air as surrogates of exercise test (29), although these were not performed in the present study. Nevertheless, neither methacholine bronchial challenge, nor EIB-test individually or combined with $FEV_1/FVC \leq 80\%$ or Bronchial lability index ≤10% confirmed EIB in more than 67% of children reporting EL. This may be related to the anti-inflammatory BHR reducing effect of ICS (16), used by many of our study subjects compared to the steroid naive children in the study by Sanchez-Garcia et al. (24).The associations between perceived EL and asthma severity and allergic disease may additionally reflect the impact of uncontrolled asthma.

In the models excluding severity and allergic disease, explained variation of perceived EL was 8.4% to 9.7%. Asthma severity score and overweight adjusted for gender; however, statistically explained 30.1% of the variance in reported EL, and in the model excluding severity; 15.5% of the variance were explained without contribution from objective measurements. Both asthma severity score and allergic disease, which are clinically accessible without objective measures, were hence advantageous to objective measures in explained variation of reported EL. Moreover, contrary to Panditi and Silverman (7) who found no association of severity and perception of exercise induced symptoms, our findings confirmed that severity assessed objectively by BHR or qualitatively by a severity score was related to perceived EL.

We found no significant associations between reported PA and perceived EL, in line with previous studies (2, 9), possibly indicating an absence of felt limitation due to inactivity or participation in PA despite perceived EL. Children and their parents may avoid symptoms through less PA, through overprotection (10) and/or beliefs that asthma limits the possibility for PA (30). On the other hand, we previously showed in the ECA study by objective recordings of PA at13 years of age that children were rather active (19, 27), indicating that children in the present study might have been rather active despite 80% reporting PA less frequently than daily.

The robust association between perceived EL and overweight was in contrast to the report by Joyner et al. (6) who found no association between BMI and self-reported EL. Pianosi and Davis (2); however, reported that overweight children with asthma perceived greater limitations of PA. Causal relationship explaining why overweight may induce limitations is complex as asthma symptoms may induce perceived EL, reduced PA level and thus development of overweight (1). We were not able to verify whether low cardiorespiratory fitness, as suggested in previous reports (5, 6, 9), may explain perceived EL in children with asthma even without BHR. However, similar fitness and PA level in overweight and normal weight children with asthma are previously reported (2). We hence interpret overweight as an independent perceived barrier of PA which may be labeled to asthma by children, irrespectively of reduced lung function, BHR, low household income, prenatal smoking, allergic disease, asthma severity score or hours/week in sports.

Strengths and limitations

The main strengths of the present study were the nested case-control design, and the assessment of perceived EL related to objective assessment of BHR and lung function through validated and standardized procedures. Lack of objective measures of PA as well as fitness, and flow volume loops during exercise indicating expiratory flow limitations are considered as a limitation, in addition to lack of parents´ and children´s reports of attitudes and beliefs about PA. Also, we asked if the child experienced exercise limitation or not, and did not include any information on grading of limitation. We were therefore unable to identify if marked EL correlated better with objective measures than did limited degree of EL. It should be underlined that results from a population based study will differ from a study based on patients referred to specialized service as the study by Vahlquist and Pedersen (1), which included patients with more severe asthma whereas the present population based study will differ as far as severity and consequences of the disease is concerned.

Conclusion

Perceived EL in children with asthma was independently associated with asthma severity and overweight, the latter doubling the probability of perceived EL irrespectively of asthma severity, allergy status, socio-economic factors, prenatal smoking or PA.

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Declaration of interest

There is no competing or conflict of interests.

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Table 1 Description of asthma severity score based on the use and dose of inhaled corticosteroids, use of leukotriene antagonists/β_2-agonists and number of exacerbations last 12 months.

	Dose of ICS (µg)			Use of LKTR and/or β_2-agonists		Number of exacerbations last 12 months			Total possible score
	0-99	100-399	$\geq$400	yes	no	0	1-3	>3	
Score	0	2	4	1	0	0	2	4	0-9

Abbreviations: ICS; inhaled corticosteroids, LKTR; leukotriene antagonist

Table 2 Descriptive characteristics of children with asthma reporting or not reporting exercise limitation (EL). Data are given as count (%) including n=294 unless otherwise stated.

	Perceived EL (n=58)	Not perceived EL (n=236)	*p*-value[a]
Boys[b]	35 (60)	152 (64)	0.57
EIB (≥ 10% fall in FEV_1) (n=264)	18 (35)	49 (23)	0.07
$R_{Max}\%FEV_1$, median (IQR) (n=264)	7 (10)	6 (6)	**0.02**
Bronchial lability index (%), median (IQR) (n=253)	10 (12)	9 (8)	0.09
Severe BHR (PD_{20} ≤1 µmol) (n=291)	17 (29)	33 (14)	**0.01**
BHR (PD_{20} ≤8) (n=291)	31 (53)	101 (43)	0.17
FEV_1 (% of predicted), mean (SD) (n=290)	94 (11)	96 (9)	0.12
FVC (% of predicted), mean (SD) (n=290)	99 (10)	98 (9)	0.91
FEV_1/FVC, mean (SD) (n=290)	83 (7)	84 (6)	**0.04**
FEF_{25-75} (% of predicted) , mean (SD) (n=290)	81 (22)	86 (19)	0.14
Low household income (< 350.000NOK /year) [c] (n=290)	16 (28)	40 (17)	0.07
Low parental education (no education beyond 13 years of schooling)	22 (38)	88 (37)	0.93
Prenatal smoking	20 (35)	50 (21)	**0.03**
Overweight	21 (36)	46 (20)	**0.01**
Allergic rhinitis only	7 (12)	23 (10)	0.60
Atopic eczema only	14 (24)	60 (25)	0.84
Allergic rhinitis + atopic eczema	24 (41)	43 (18)	**<0.01**
Asthma severity score, median (IQR)	5 (5)	0 (3)	**<0.01**
Use of ICS last 12 months	37 (64)	46 (20)	**<0.01**
Hours / week in sports, median (IQR)	2 (3)	2 (2)	0.16
Daily physical activity	13 (22)	41 (18)	0.39

[a] statistical differences between groups in bold. Analysis conducted: categorical variables; Chi-square tests, continuous normally distributed variables; independent t-tests, skewed variables; Mann-Whitney Wilcoxon tests. Statistical significant differences at 5% level are given in bold.

[b] with reference to girls

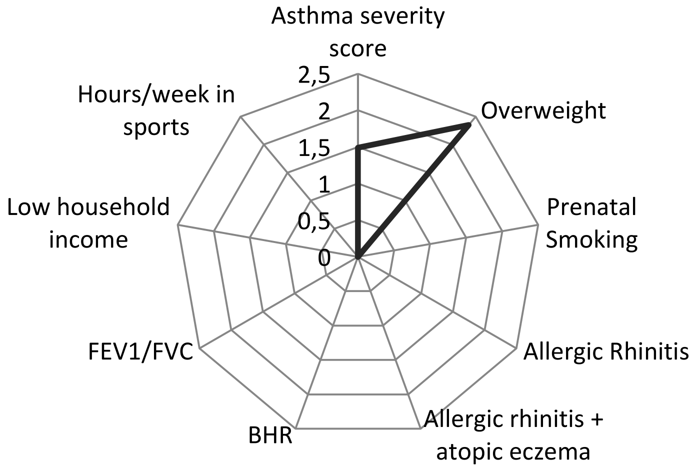
[c] corresponding to ≈ 43000 €

Abbreviations: n; numbers, EIB; exercise induced bronchoconstriction, FEV_1; forced expiratory volume in 1 second, $R_{Max}\%FEV_1$; maximal reduction in FEV_1 post exercise (%), IQR; interquartile range, BHR; bronchial hyper responsiveness, SD; standard deviation, FVC; forced vital capacity, FEF_{25-75}; forced expiratory flow at 25-75% of FEV_1, NOK; Norwegian Kroner, ICS; inhaled corticosteroids.

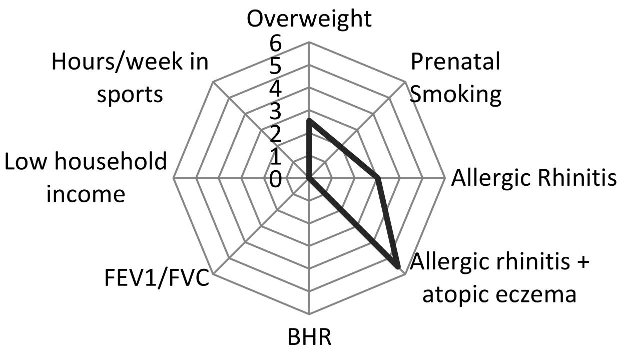
Figure 1 Radar plots visualizing Odds ratio (OR) of factors associated with perceived exercise limitation (EL) in children with asthma showing (A) a total model with explained variance of 30.1% in EL including a composite Asthma severity score (use of asthma medication and asthma exacerbations) and (B) a model excluding the Asthma severity score with explained variance of 15.5% in EL. Numbers from 0 to 2.5 (A) and 0 to 6 (B) illustrate the OR for reporting EL. Models were adjusted for gender. The least significant variables were removed stepwise according to Hosmer et al (22) until only significant variables remained.

Fig. 1.

(A)



(B)

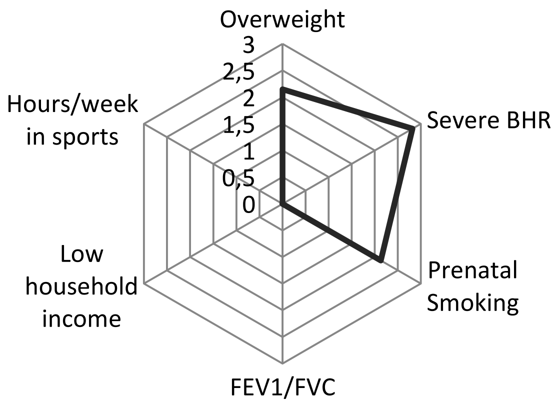


Abbreviations: BHR; bronchial hyper responsiveness, FEV_1; forced expiratory volume in 1 second, FVC; forced vital capacity

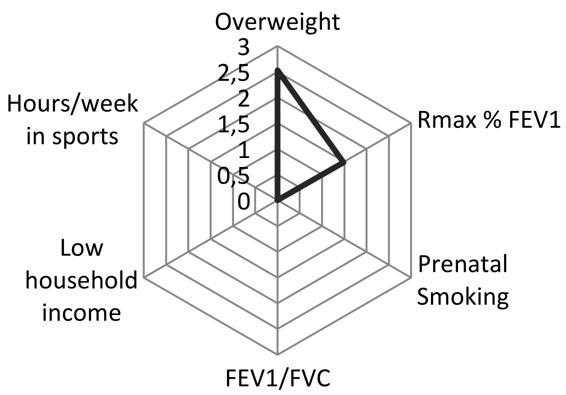
Figure 2 Radar plots visualizing Odds ratio (OR) of factors associated with perceived exercise limitation (EL) in children with asthma using Severe BHR (B) and $R_{Max}\%FEV_1$ (A) to assess BHR in separate reduced multivariate logistic regression models excluding asthma severity and allergic disease from analysis. Model including Severe BHR (A) explained 9.7%, and model including $R_{Max}\%FEV_1$ (B) explained 8.4% of the variance in EL, respectively. Numbers from 0 to 3 illustrate the Odds Ratio for reporting EL. Models were adjusted for gender. The least significant variables were removed stepwise according to Hosmer et al (22) until only significant variables remained.

Fig. 2.

(A)



(B)



Abbreviations: FEV_1; forced expiratory volume in 1 second, FVC; forced vital capacity, $R_{Max}\%FEV_1$; maximal reduction in FEV_1 post exercise (%), BHR; bronchial hyper responsiveness.