Effect of age on exercise-induced bronchoconstriction in children and adolescents with asthma

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Objective: The relationship between exercise-induced bronchoconstriction (EIB) and exertional dyspnea in children and adolescents is yet to be fully established. This study examined whether indicators of fractional exhaled nitric oxide (FeNO), forced expiratory volume in 1 s (FEV_1) percent predicted at baseline, and dyspnea are useful for predicting children and adolescents with EIB.

Methods: We enrolled 184 children and adolescents diagnosed with asthma (mean age 11.2 years); participants were divided into two groups according to age (12 years) and were subjected to a 6-min exercise challenge test. Lung function tests and modified Borg scale scores were used to examine perceptions of dyspnea at 0, 5 and 15 minutes after exercise.

Results: Among children, the maximum percentage drop in FEV_1 after exercise correlated significantly with FeNO (adjusted $\beta = 2.3$, $P < 0.001$) and with the perception of dyspnea at 5 minutes after exercise (adjusted $\beta = 1.9$, $P < 0.001$). Among adolescents, the maximum percentage drop in FEV_1 correlated with FeNO (adjusted $\beta = 2.7$, $P = 0.007$) and with lung function (FEV_1, percent predicted; adjusted $\beta = -0.28$, $P = 0.006$). Children with EIB had significantly stronger dyspnea after exercise than did children without EIB. Adolescents even without EIB may experience more exertional dyspnea than children without EIB.

Conclusions: Overall, our findings indicated that EIB was associated with FeNO and exertional dyspnea in asthmatic children. By contrast, EIB was associated with FEV_1 percent predicted at baseline and FeNO but not with exertional dyspnea in asthmatic adolescents.

Introduction

Many asthmatic children are thought to have exercise-induced bronchoconstriction (EIB) (1). Asthmatic children with EIB tend to be physically passive and participate only infrequently in physical activity and play (2). A recent systematic review of the epidemiologic literature on this subject revealed that children with low levels of physical activity have up to a 35% increased risk of new-onset asthma and/or wheezing (3). As such, given the negative influence of EIB on quality of life and psychomotor development (4, 5), identification of asthmatic children with EIB is an important consideration for pediatricians. Therefore, there is a need for a simple index that can be used to identify children with or without EIB for whom exercise testing may not be required.

The fractional concentration of nitric oxide (FeNO) is measured by non-invasive methods and is used to evaluate airway inflammation in patients with asthma. We have observed that airway hyperresponsiveness in response to acetylcholine is associated with obstruction of the lower airways, whereas in adolescents diagnosed with asthma (6). In contrast, airway hyperresponsiveness has been associated with airway inflammation in children with asthma. Several studies have documented a relationship between FeNO and EIB (7, 8, 9). Even parent-reported respiratory symptoms during exercise have been found to have no correlation with the severity of clinically-diagnosed EIB (10).

The Borg scale (11) is usually used to determine the rate of perceived exertion globally. Dyspnea can be measured via several methods. The modified Borg scale can be useful scale for perception dyspnea during and after exercise together with the Borg scale (12). We chose the modified Borg scale for dyspnea because it could be used together with the Borg scale for perceived exertion in the same sheet. The relationship between perception of dyspnea during exercise and EIB has not yet been fully established in children and adolescents diagnosed with asthma. The International Study of Asthma and Allergies in Childhood questionnaire revealed that the prevalence of exercise-induced wheezing was as high as 17.9% for junior high school students in Japan (13). The present study aims to determine indicators of fractional exhaled nitric oxide (FeNO), forced expiratory volume in 1 s (FEV_1) percent predicted at baseline, and dyspnea are useful for predicting children and adolescents with EIB.

Methods

Study subjects

A total of 184 participants (120 boys, 64 girls; mean age, 11.2, range 6-18 years) who were diagnosed with bronchial asthma and suspected of having EIB based on sensations of dyspnea, cough, and/or wheezing during exercise were recruited from the outpatient clinic of the Department of Pediatrics of the National Hospital Organization Fukuoka National Hospital. The primary diagnosis of bronchial asthma was clinically defined using episodic symptoms of airflow obstruction or airway hyperresponsiveness and reversible airflow obstruction based on guidelines established by the Global Initiative for Asthma (14). All subjects had well-controlled and clinically stable asthma at the time of this study. Patients with a history of respiratory viral infections or asthma exacerbations within a period of one month preceding the exercise challenge test were excluded. None of the subjects were smokers. Of note, 54 of the participants enrolled in this study were receiving treatments that included inhaled corticosteroids (ICS). Parental and participants' written informed consent was obtained from each enrolled individual. The study was approved by the Ethics Board of the National Hospital Organization Fukuoka National Hospital (No.20-3).

Study design

ICS, inhaled long-acting β-agonists (LABA), leukotriene receptor antagonists and antihistamines were withheld for at least 24 h prior to the test, whereas short-acting β2-

agonists were withheld for at least 8 h prior to the test. Subjects underwent a physical examination, blood collection and FeNO measurement before starting the standardized exercise test.

Blood samples

The serum immunoglobulin E (IgE) levels were measured using enzyme-linked immunosorbent assays for the detection of total IgE and Dermatophagoides pteronyssinus specific IgE antibodies within one year before exercise challenge.

FeNO value

FeNO was measured using a chemiluminescence analyzer (model 280, Nitric Oxide Analyzer; Sievers Instruments, Boulder, CO, USA). All subjects underwent online (real-time) FeNO measurements prior to the exercise challenge test. Online FeNO measurements were performed according to the recommendations of the European Respiratory Society/American Thoracic Society (15).

Lung function measurements, exercise challenge and evaluation of dyspnea and exertion after exercise

Spirometry measurements were performed using a hot-wire spirometer (Chestgraph HI-701; Chest Ltd., Tokyo, Japan). Forced expiratory maneuvers were repeated until two acceptable values of the forced expiratory volume in 1 s (FEV_1) were obtained; the larger value was used in the analysis in accordance with the guidelines of the American Thoracic Society (16). We recorded values for FEV_1, forced vital capacity (FVC), peak expiratory flow (PEF) and forced expiratory flow at 50% of the FVC (FEF_{50}) as percentages of predicted values for the Japanese population as reported previously (17). Those with a predicted FEV_1 at baseline <70% were excluded from the exercise challenge test.

Two main methods were used for exercise testing in children and adolescents, namely the treadmill and the cycle ergometer, with each method having its advantages and disadvantages. Children consistently reported that they were more comfortable on the cycle ergometer than on the treadmill (18). Furthermore, electrocardiogram findings were easier to assess and were of better quality when using the cycle ergometer. Exercise was performed using a cycle ergometer (Bosch Erg 551, Germany) for 6 min with the workload set at 2.1 W/kg; heart rates were monitored throughout the exercise period. During the test, the cycle ergometer speed was increased to induce a heart rate of at least 80% of the child's maximal predicted heart rate (maximal heart rate = 210 - age).

Subjects assigned themselves Borg scale scores during the exercise challenge test, which provided information on perceived levels of exertion and associated dyspnea (11). After each FEV_1 measurement performed during the exercise challenge test, each patient determined his or her perceived exertion using a Borg scale score ranging from 6 to 20. Perceptions relating to dyspnea were evaluated using a modified Borg scale ranging from 0 to 10 that was devised to measure the degree to which subjects perceived the severity of dyspnea after exertion; a score of zero on the scale represents the perception of no dyspnea. Lung function and Borg scales were assessed before exercise and 0, 5 and 15 min after exercise (19). A 15% post-exercise drop in FEV_1 cut-off was considered to indicate a diagnosis of EIB (20).

Statistical analysis

Age, height, weight, baseline lung function and maximum percentage drop in FEV_1 after exercise were presented as the mean (standard deviation; [SD]). Overweight children were defined as those having a body mass index >75 percentile for age and gender using standardized charts from the Japanese Centers for Disease Control and Prevention (21). Serum IgE and FeNO were presented as geometric means with 95% confidence intervals (CIs). Differences between children and adolescents with respect to the aforementioned values were assessed using the Mann-Whitney *U*-test for continuous variables and Fisher's exact test for categorical variables. Spearman rank correlation coefficients were used to assess the relationships between FEV_1, FeNO, and perception of dyspnea at 5 minutes after the exercise challenge test. A *P* value <0.05 was considered significant. Multiple linear regressions were used to evaluate the associations between selected measures for FEV_1, FeNO, and perception of dyspnea at 5 minutes after exercise as independent variables with respect to the exercise challenge test. FeNO values were subjected to log2 transformations to normalize the distributions prior to their use in the regression analyses. Both crude and gender-based ICS treatment-adjusted regression coefficients were obtained. A two-tailed *P* value <0.05 was considered significant. All analyses were performed using STATA version 14.0 (Stata Corp; College Station, TX, USA).

Results

The 184 participants enrolled in the study were evaluated using the exercise challenge test. This group included 113 children (<12 years of age) and 71 adolescents (≥12 years of age). A flow chart for this study group is shown in Fig. 1; subject characteristics and test results are summarized in Tables 1 and 2, respectively. The prevalence of ICS treatment, number of non-atopic individuals, serum total IgE levels and lung function at baseline were determined for both groups. The percent predicted PEF was lower among adolescents than it was among children (104% [SD, 19] vs. 112 % [SD, 27]; $P = 0.02$), while FeNO values were significantly higher among adolescents than they were among children (43 parts per billion [ppb]; 95% CI, 34–54 ppb *vs*. 32 ppb; 95% CI, 27–38 ppb; $P = 0.03$). Maximum percent drop in FEV_1 was not significantly different when comparing the two groups (Table 2).

Subsequently, changes in FEV_1 and perception of dyspnea (Fig. 2) after exercise challenge (Fig. not shown) were presented according to the presence or absence of a diagnosis of EIB among those in both groups. Accordingly, children diagnosed with EIB (i.e. those with maximum percent drop in $FEV_1 \geq 15\%$, n = 29) showed significantly stronger perceptions of dyspnea than did children who were not diagnosed with EIB (Fig. 2c). Dyspnea perception scores were 4 [Interquartile range(IQR): 2.5–5.8], 2 (IQR: 1–4) and 0.5 (IQR: 0–2) at 0, 5, and 15 minutes, respectively, after exertion among children with EIB and 3 (IQR: 1–4), 0.6 (IQR: 0–2) and 0 (IQR: 0–0.5) at these same time points after exercise, respectively, among EIB-negative children ($P < 0.01$, $P < 0.001$ and $P < 0.05$, respectively). By contrast, the results in Fig. 2d indicate that there were no differences with respect to the perception of dyspnea after exercise when comparing results from EIB-positive and EIB-negative adolescents. EIB-positive adolescents showed similar changes with respect to perceptions of dyspnea (Fig. 2d) when compared with results from EIB-negative adolescents.

A comparison among EIB-negative participants revealed that the perception of dyspnea was higher among adolescents, with scores of 3 (IQR: 2-5) and 1 (IQR: 0.5-3) at 0 and 5 min after exercise (Fig. 2d), respectively, than was observed among children at the same time points (Fig. 2c) [3 (IQR: 1-4), $P = 0.023$ and 0.6 (IQR: 0-2), $P = 0.027$]. No differences were observed in FEV_1 when comparing EIB-negative children and adolescents. Subjects with an EIB-positive response to exercise showed similar changes in bronchoconstriction and perception of dyspnea regardless of their age.

The findings presented in Table 3 summarize the associations between pulmonary function, FeNO, and perception of dyspnea at 5 min after the exercise challenge test in both groups. Among children, increased maximum percent drop in FEV_1 after exercise was associated with higher FeNO (r = 0.24; adjusted $\beta = 2.3$; $P < 0.001$; Fig. 3c). This finding implies that for every change in maximum percent drop in FEV_1, we observed a 2.3 log2 change in FeNO. Maximum percent drop in FEV_1 was associated with the perception of dyspnea at 5 min after exercise (r = 0.35; adjusted $\beta = 1.9$; $P < 0.001$; Fig 4a) but was not associated with predicted FEV_1 (Fig. 3a).

Among adolescents, the maximum percent drop in FEV_1 after exercise was significantly associated with both FeNO (r = 0.25; adjusted β = 2.7; *P* = 0.007; Fig. 3d) and predicted FEV_1 (r = −0.3; adjusted β = −0.28; *P* = 0.006; Fig. 3b). No significant relationships were observed between perceptions of dyspnea at 5 min and the maximum percent drop in FEV_1 after exercise among adolescents (Fig. 4b).

Discussion

There is some evidence that supports the hypothesis that eosinophilic airway inflammation is associated with EIB in all asthmatic children (6, 22- 24). In the present study, EIB was associated with airway inflammation in both asthmatic children as well as in adolescents; FeNO levels were higher in adolescents than in the children. This finding is consistent with observations that report FeNO increasing with age in healthy children (25). Regardless of age, EIB in asthmatic children may include a transient or inducible component that reflects the acute impact of airway inflammation. Among adolescents with asthma, EIB has been associated with both FEV_1 percent predicted at baseline and airway inflammation. The persistent factor in asthmatic adolescents may be closely related to FEV_1 percent predicted at baseline that represents the initiation of structural airway changes. The baseline state underlying this persistent factor likely reflects FEV_1 percent predicted at baseline that develops in response to the chronic effects of airway inflammation (6). As such, the degree of FEV_1 percent predicted at baseline present at baseline probably reflects the chronicity of the disease. The mechanisms of airway remodeling include increased airway wall thickness and increased airway smooth muscle mass, both leading to reduced airway caliber. Interestingly, results from our study suggest that structural abnormalities arising from chronic airway inflammation are associated with EIB severity among adolescents but not among children. A small study conducted on adults reported no relationship between baseline FEV_1 percent predicted and EIB (9). Previous studies have shown that some people may have very subtle differences in respiratory impedance without marked changes in lung function (26).

In the present study, the perception of dyspnea after exertion was associated with EIB severity among asthmatic children but not among asthmatic adolescents. Strenuous exercise has been shown clearly to be associated with an increased risk of developing asthma; this conclusion assumes a dose–response relationship between physical activity and EIB risk with a U-shaped curve that indicates that moderate exercise training leads to a lower risk for asthma compared to high-intensity exercise training, notably both endurance and interval training (1). The level of physical activity was closely related to physical fitness in children, while time engaged in vigorous activity was related to physical fitness in adolescents (27). Accordingly, given the little variation in both high intensity exercise and physical fitness in childhood, the severity of EIB affects the perception of dyspnea during exercise. These findings might explain the differences in perception of dyspnea during exercise noted between asthmatic adolescents with relatively low physical activity and those participating in daily vigorous activity regardless of EIB severity (28).

The qualitative description of dyspnea may contain important information regarding the mechanisms underlying its intensity (29). One study has shown that asthmatic adults experience chest tightness mainly after methacholine inhalation testing (30), although they experience inspiratory effort primarily after short trials of cardiopulmonary exercise testing. During short-duration cardiopulmonary exercise testing, there is a positive relationship between Borg score and minute ventilation. In the present study, adolescents without EIB showed greater perceptions of dyspnea perception than did children without EIB. As such, when asthmatic children develop into adolescents, both the Borg dyspnea scale and minute ventilation during exercise may increase even without EIB. Obesity increases minute ventilation and perception of dyspnea due to physical activity (31). However, the current study found no difference in the rate of overweight between children and adolescence. Further detailed studies are therefore warranted to identify factors that are involved in dyspnea during exercise, especially in adolescents.

Our study has some limitations. First, we did not use a standard source of cold dry air during the exercise challenge test because the indoor temperature and humidity maintained by air-conditioning at the testing site were adequate for a suitable exercise challenge. Second, we measured lung function only at 0, 5 and 15 min after exercise and did not follow the full set of guidelines from the ATS/ERS; instead, we used methods established in our country for the evaluation of asthmatic children which involve many challenge tests over a shorter period of time (19, 24).

Conclusions

In summary, the results of our study revealed that EIB was associated with FeNO and exertional dyspnea but not with FEV_1 percent predicted at baseline among children diagnosed with asthma. On contrary, among adolescents with asthma, EIB was associated with both FEV_1 percent predicted at baseline and FeNO but not with exertional dyspnea. Adolescents without EIB may experience more exertional dyspnea than children without this diagnosis.

We therefore recommend that pediatricians should consider EIB in adolescent cases with both lower FEV_1 percent predicted at baseline and higher FeNO regardless of whether perception dyspnea exists during exercise. Future research should explore a comparison between exertional dyspnea associated with EIB in both asthmatic children and adolescents, which is certainly another important area of concern.

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Table 1. Subject Characteristics and Differences According to Age

Parameters	Total Subjects	Children (<12yr old)	Adolescents (≧12yr old)	p Value
Case, No.	184	113	71	
Male gender, No (%)	120(65)	77(68)	43(61)	0.29
Mean age (range), yr	11.2(6-18)	9.5(6-11)	13.9(12-18)	
Mean height (range), cm	144(106-181)	135(106-164)	158(134-181)	
Mean weight (range),kg	39(18-81)	32(18-57)	50(30-81)	
Overweight+, No (%)	44 (24)	24 (21)	20 (28)	0.31
Received ICS, No (%)	54(29)	33(29)	21(30)	0.96
Nonatopic cases, No (%)*	6(3)	4(4)	2(3)	0.79
Geometric mean serum IgE (95%CI), kU/L	512(400-650)	559(430-740)	432(260-710)	0.70
Low specific IgE against house-dust mite cases, No. (%)	11(6)	6(5)	5(7)	0.63

IgE, immunoglobulin E.

+Overweight children were defined as those having a body mass index >75 percentile as compared with the sex-specific Centers of Disease Control growth curve [15].

* Nonatopic case: low IgE(<100 kU/L) and low specific IgE(<0.7 kU/L) against Dermatophagoides pteronyssinus.

Table2. Differences in Pulmonary function, fractional exhaled nitric oxide (FeNO), and exercise challenge test According to Age

Parameters	Total Subjects	Children(<12yr old)	Adolescents(≧12yr old)	p Value
Lung function at baseline				
FVC, % predicted, %	101 (14)	100 (14)	102 (13)	0.22
FEV_1,% predicted, %	95 (12)	94 (12)	97 (13)	0.07
FEV_1/FVC, %	82 (7)	82 (8)	83 (7)	0.15
Peak expiratory flow (% predicted), %	109 (24)	112 (27)	104 (19)	0.02
FEF_{50} (% predicted), %	88 (23)	87 (24)	90 (22)	0.47
Geometric mean FENO (95%CI), ppb	36 (31-41)	32 (27-38)	43 (34-54)	0.03
Exercise challenge test				
Mean max %drop in FEV_1 after exercise ,%	8.9（-15-53）	9.5（-8-53）	8.0（-15-46）	0.41
EIB positive* cases, No. (%)	43 (23)	29 (26)	14 (20)	0.36
Max heart rate in exercise/min.	175 (21)	178 (11)	172 (30)	0.057
Median rate of perceived exertion (IQR) after exercise	13 (12–15)	13 (12–16)	13.5 (12–15)	0.87
Median perception of dyspnea at 5min after exercise (IQR)	1 (0.5-3)	1 (0-3)	2 (0.5-3)	0.15

Data are presented as mean (SD), unless otherwise stated. FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; FEF50, forced expiratory flow at 50% of the FVC; IQR, interquartile range.

* Max %drop in FEV1 ≧15%

Table3.Association of pulmonary function, fractional exhaled nitric oxide (FeNO) and perception of dyspnea with Exercise challenge test for two groups according to Age

Parameters	Spearman Correlation	Regression Coefficient					
	Coefficient	Crude β	95%CI	p Value	Adjusted β*	95%CI	p Value
Children(<12yr old)							
FEV1,% predicted	-0.08	-0.09	-0.22, 0.04	0.16	-0.09	-0.22, 0.04	0.17
FeNO	0.24	2.3	1.04, 3.56	<0.001	2.3	1.04, 3.64	<0.001
Perception of dyspnea 5min after exercise	0.35	1.9	0.97, 2.74	<0.001	1.9	1.0, 2.8	<0.001
Adolescents(≧12yr old)							
FEV1, % predicted	-0.3	-0.29	-0.48, -0.09	0.005	-0.28	-0.48, -0.08	0.006
FeNO	0.25	2.7	0.81, 4.59	0.006	2.7	0.78, 4.68	0.007
Perception of dyspnea 5min after exercise	0.21	1.1	-0.43, 2.56	0.16	1.1	-0.54, 2.64	0.19

FEV1, Forced expiratory volume in 1 s.

*Adjusted for gender and inhaled corticosteroid treatment

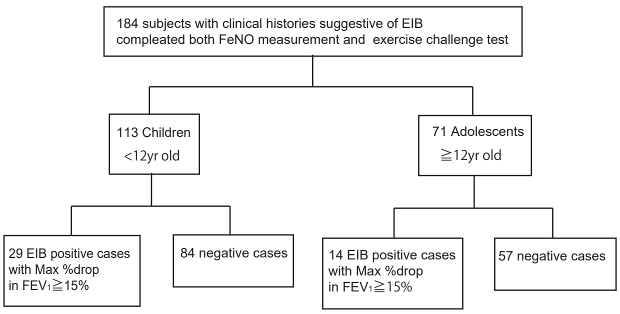

Figure 1. Study group flowchart. EIB = exercise-induced bronchoconstriction; FeNO = fraction of exhaled nitric oxide, FEV1 = forced expiratory volume in 1 s.

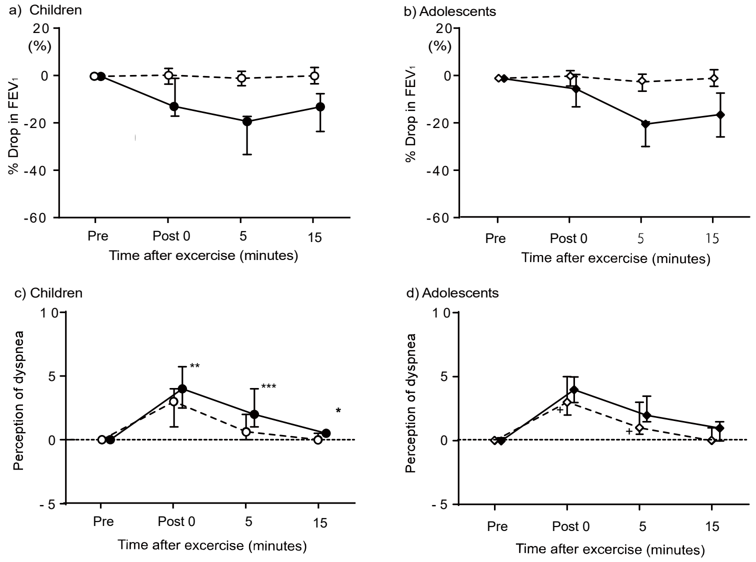

Figure 2. Changes in forced expiratory volume in 1 s (FEV1) and perception of dyspnea before and after exercise in asthmatic children and adolescents with positive (closed symbols and solid lines) or negative (opened symbols and dotted lines) diagnosis of exercise-induced bronchoconstriction (EIB). Bars indicate mean ± standard deviation (SD) in a) and b) and the median ± interquartile range (IQR) in c) and d). *P<0.05, **P<0.01, ***P<0.001, and+P<0.05. Each values were compared to values in children with negative diagnosis of EIB. (a) Changes in FEV1 after exercise (children), (b) Changes in FEV1 after exercise (adolescents), (c) Changes in perception of dyspnea (children), (d) Changes in perception of dyspnea (adolescents).

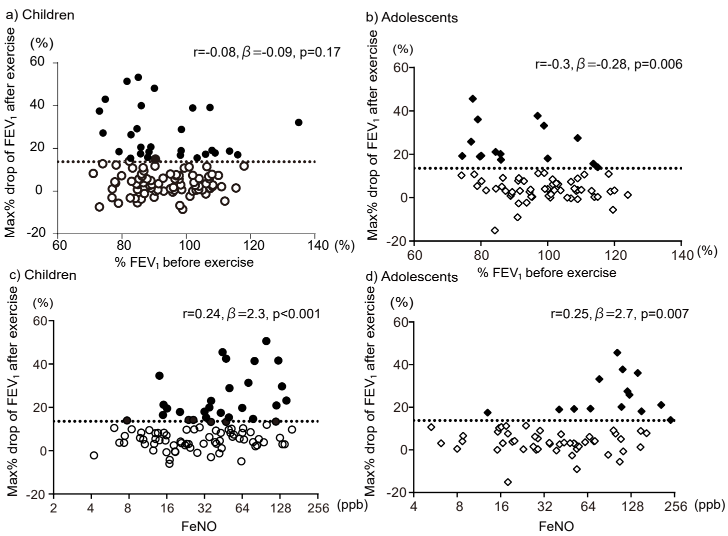

Figure 3. Relationship between max % drop in forced expiratory volume in 1 s (FEV1), % FEV1 before exercise and fraction of exhaled nitric oxide (FeNO) in asthmatic children and adolescents. Closed and open symbols indicate asthmatic patients with and without exercise-induced bronchoconstriction, respectively. (a) Relationship between max % drop of FEV1 and % FEV1 before exercise (children), (b) Relationship between max % drop of FEV1 and % FEV1 before exercise (adolescents), (c) Relationship between max % drop of FEV1 before exercise and FeNO (children), (d) Relationship between max % drop of FEV1 before exercise and FeNO (adolescents)

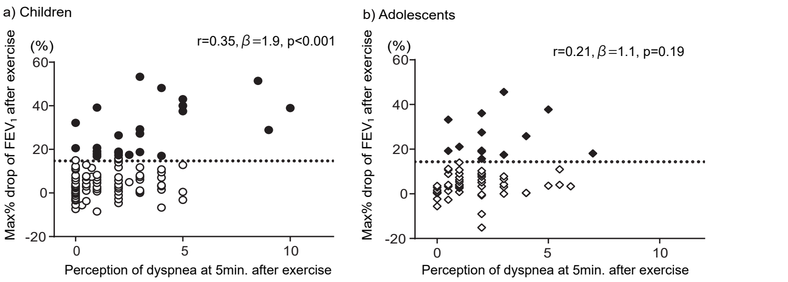

Figure 4. Relationship between max % drop in forced expiratory volume in 1 s (FEV1) and perception of dyspnea 5 min after exercise in asthmatic children and adolescents. Closed and open symbols indicate asthmatic patients with and without exerciseinduced bronchoconstriction, respectively. (a) Children, (b) Adolescent.