

Monitoring pulmonary function during exercise in children with asthma

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ABSTRACT

Objective Exercise-induced bronchoconstriction (EIB) is defined as acute, reversible bronchoconstriction induced by physical exercise. It is widely believed that EIB occurs after exercise. However, in children with asthma the time to maximal bronchoconstriction after exercise is short, suggesting that the onset of EIB in such children occurs during exercise.

Aim In this study the authors investigate pulmonary function during exercise in cold air in children with asthma.

Methods 33 Children with asthma with a mean age of 12.3 years and a clinical history of exercise induced symptoms, underwent a prolonged, submaximal, exercise test of 12 min duration at approximately 80% of the predicted maximum heart rate. Pulmonary function was measured before and each minute during exercise. If EIB occurred (fall in forced expiratory volume in 1 s >15% from baseline), exercise was terminated and salbutamol was administered.

Results 19 Children showed EIB. In 12 of these children bronchoconstriction occurred during exercise (breakthrough EIB), while seven children showed bronchoconstriction immediately after exercise (non-breakthrough EIB). Breakthrough EIB occurred between 6 and 10 min of exercise (mean 7.75 min).

Conclusion In the majority of children with EIB in this study (ie, 12 out of 19), bronchoconstriction started during, and not after, a submaximal exercise test.

INTRODUCTION

Exercise-induced bronchoconstriction (EIB) is common in children and adolescents with asthma and is associated with an impaired quality of life.¹

EIB is defined as acute, reversible bronchoconstriction occurring 5–15 min after cessation of physical exercise.^{2–3} It is suggested that EIB is caused by exercise induced drying of the respiratory mucosa, leading to degranulation of mast cells and subsequent release of inflammatory mediators. These mediators interact with effector cells (eg, smooth muscle cells) and lead to bronchoconstriction.⁴ Another proposed mechanism for EIB is that exercise induced hyperpnoea causes airway cooling. After exercise, when hyperpnoea ceases, the airways rapidly rewarm, leading to engorgement of the hyperplastic vascular bed in the asthmatic airway wall and subsequent bronchoconstriction (thermal hypothesis).⁵ Exercise also induces the release of several bronchodilating mediators, such as prostaglandin PGE₂ and nitric oxide, protecting against bronchoconstriction. In addition, exercise induced deep inspirations lead

What is already known on this topic

- ▶ Exercise-induced bronchoconstriction (EIB) is defined as acute, reversible bronchoconstriction occurring after exercise.
- ▶ In adults with asthma, prolonged exercise (>15 min) can elicit bronchoconstriction during exercise.
- ▶ In children with asthma, the time to maximal bronchoconstriction after exercise is short, suggesting that the onset of EIB in children occurs during exercise.

What this study adds

- ▶ Monitoring pulmonary function in children with asthma during exercise is feasible.
- ▶ In the majority of studied children with asthma, EIB started during, and not after, exercise.
- ▶ Measuring pulmonary function during exercise provides additional clinical information, as breakthrough EIB compromises participation in sports and active play and indicates uncontrolled asthma.

to increased mechanical stretching of the airway smooth muscle, bronchodilating the lower airways.⁶ Indeed exercise is a potent bronchodilator once bronchoconstriction has set in.^{3,7} Thus there is a balance between bronchoconstrictor and bronchodilator influences, preventing EIB during exercise. However, several studies in adults with asthma demonstrated that prolonged exercise (>15 min) can trigger EIB during exercise.^{2,8–11} Previous studies have shown that the time to maximal bronchoconstriction after exercise is shorter in children with asthma than in adults with asthma.^{12,13} This rapid fall in forced expiratory volume in 1 s (FEV₁) after exercise leads us to hypothesise that EIB in children with asthma starts during exercise, contrary to the widely held belief that EIB occurs after exercise. The aim of the present study was to investigate pulmonary function during exercise in cold air in children with asthma.

METHODS

Subjects

Thirty-three children (23 male, 10 female) with a mean age of 12.3 years (range 8–15) and

with a clinical history of exercise induced symptoms were investigated in this study. Exercise tests were performed as part of the routine clinical evaluation, although with the addition of spirometry during exercise. No short- or long-acting bronchodilators were used 8 or 24 h, respectively, before testing. None of the children had used oral steroids for at least 3 weeks before the study. Inhaled corticosteroids and leukotriene antagonists were not withheld before testing. All of the children were informed and the local ethics committee was consulted but did not object to the study.

Pulmonary function measurements

The children underwent extensive evaluation of their asthma, which consisted of an exercise provocation challenge, Juniper's Asthma Control Questionnaire and measurement of the fraction of exhaled nitric oxide using the miniNIOX (Aerocrine, Stockholm, Sweden).

Standard lung function tests were performed before, during and after exercise, using a Microloop MK8 Spirometer (ML3535; CareFusion 232, Chatham Maritime, UK). Before exercise, spirometry consisted of a duplicated full flow volume curve, using the standard European Respiratory Society (ERS) protocol.¹⁴ The best value for FEV₁ was used for analysis. During and after exercise, spirometry was limited to a single flow volume curve. Only technically correct flow volume curves were used for statistical analysis.

Exercise provocation challenge

After baseline spirometry, subjects performed a prolonged exercise test by running with their nose clipped on a treadmill with a 10% incline (Ti22; Horizon Fitness, Cottage Grove, Wisconsin, USA). Conducting the tests in a local skating rink in IJssbaan Twente, Enschede, The Netherlands ensured that air was cold and dry with a temperature of 9.5–10.0°C and humidity of 57–59% (5.5–6.0 mg H₂O/l). The ice was resurfaced with electric resurfacing machines. During the test, heart rate was continuously monitored by a radiographic device (Inventum SH 40, Veenendaal, the Netherlands). The children performed a constant-load exercise test at approximately 80% of the predicted maximum heart rate (210–age).¹⁵ During the

exercise challenge, single flow volume curves were recorded every minute. The maximum duration of the exercise test was 12 min or until a fall in FEV₁ >15% from the baseline value had occurred. In this case the challenge was terminated, one flow volume curve was measured 1 min after cessation and salbutamol 100 µg was administered immediately after spirometry or at request. In children who completed 12 min of exercise, spirometry was obtained at 1, 3 and 5 min after exercise. If EIB (fall in FEV₁ >15%¹³) occurred during this period, salbutamol 100 µg was administered immediately after this measurement. To establish recovery, one flow volume curve was measured approximately 10 min after administration of salbutamol.

Statistical analysis

Results were expressed as mean values±SD for normally distributed data, as median (minimum to maximum) for non-normally distributed data or as numbers with corresponding percentages if nominal or ordinal. The level of significance was set at 0.05 (95% CI). Between-group comparison of continuous data was performed by analysis of variance or Kruskal–Wallis tests as appropriate, and a post hoc test for statistically significant differences was performed with Tukey's HSD test. Comparisons of nominal or ordinal variables were performed with χ^2 tests. SPSS for Windows v 15 was used to perform all analyses.

RESULTS

Thirty-three children participated in the study. Two children were unable to complete the test because test instructions were not followed and one child was excluded because of technical problems during the test (heart rate monitor malfunction). Thirty children were included in the analysis. All children were able to perform spirometry during exercise. Flow volume curves were technically acceptable and no signs of fatigue or spirometry-induced bronchoconstriction were observed.

Nineteen children (11 male, eight female) showed EIB (fall in FEV₁ >15% from baseline value). In 12 of these children (six male, six female), EIB occurred during exercise (breakthrough EIB). Seven children showed EIB immediately after exercise (non-breakthrough EIB). Eleven children did not show EIB.

Table 1 Baseline characteristics of breakthrough exercise-induced bronchoconstriction (EIB), non-breakthrough EIB and non-EIB groups

Characteristics	Breakthrough EIB (N=12)	Non-breakthrough EIB (N=7)	Non-EIB (N=11)	p Value
Age (years)	11.6 (8.2–15.3)	12.5 (11.5–14.2)	12.6 (9.3–15.0)	0.51
Male	6 (50)	5 (71)	9 (82)	0.62
BMI z score	0.8 (–0.4 to 2.4)	0.6 (–1.4 to 2.2)	0.7 (–0.8 to 1.3)	0.65
ICS	12 (100)	6 (86)	8 (73)	0.16
Fluticasone 250 µg 2 bd	3	2	0	
Beclomethasone 100 µg 2 bd	1	1	1	
Budesonide 200 µg 2 bd	0	0	1	
Ciclesonide 160 µg 1 bd	0	0	2	
LABA (combination therapy)	8 (67)	3 (43)	4 (36)	0.32
Budesonide/formoterol 200/6 µg 2 bd	4	3	2	
Fluticasone/salmeterol 250/50 µg 2 bd	4	0	2	
LTRA	4 (33)	3 (43)	5 (46)	0.83
FeNO (ppb)	28 (11–84)	31 (14–119)	30 (11–48)	0.66
ACQ	1.3 (0.3–3.2)	2.0 (1.0–3.2)	1.2 (0.0–1.8)	0.31
FEV ₁ (% predicted)	83.3±9.2	86.7±11.7	89.7±12.9	0.40
Mean HR during exercise	75.7±2.8	78.5±1.6	79.5±2.9	<0.01

Results are expressed as median (minimum to maximum), mean values±SD or as numbers (percentages).

ACQ, Asthma Control Questionnaire; BMI, body mass index; FeNO, fraction exhaled nitric oxide; FEV₁, forced expiratory volume in 1 s; HR, heart rate (% of maximum); ICS, inhaled corticosteroid; LABA, long acting bronchodilator agent; LTRA, leukotriene antagonist (montelukast 1 dd 5 mg); bd, twice daily.

Table 2 Individual characteristics of the breakthrough exercise-induced bronchoconstriction (EIB) group

Subject	Sex	Age (years)	Height (cm)	BMI z score	ICS	LABA	LTRA	Baseline FEV ₁ (% predicted)	Time to ↓FEV ₁ >15% (min)	↓FEV ₁ at cessation (% from baseline)	↓FEV ₁ t=1 (% from baseline)
1	F	11	156	1.3	+	-	+	81	7	-15	-47
2	F	8	137	1.2	+	-	+	91	6	-24	-28
3	F	9	141	0.1	+	+	-	84	6	-23	-54
4	F	8	132	2.0	+	+	-	74	6	-35	-45
5	M	15	168	1.9	+	+	-	89	8	-16	-32
6	M	12	155	-0.1	+	+	-	67	10	-18	-27
7	F	10	140	1.7	+	+	+	96	10	-17	-34
8	F	14	165	-0.4	+	-	+	84	8	-15	-34
9	M	11	138	0.4	+	+	-	85	9	-15	-45
10	M	11	162	0.1	+	+	-	69	10	-17	-17
11	M	13	163	2.4	+	-	-	94	6	-15	-21
12	M	13	175	-0.2	+	+	-	85	7	-19	-26

↓FEV₁ at cessation, fall in FEV₁ at cessation of exercise; ↓FEV₁ t=1, fall in FEV₁ 1 min after exercise; BMI, body mass index; F, female; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABA, long acting bronchodilator agent; LTRA, leukotriene antagonist; M, male; time to ↓FEV₁ >15%, time to EIB during exercise.

The baseline characteristics of the children are shown in table 1. Body mass index (BMI) was adjusted for age and gender and calculated as SD from the mean (BMI z score).¹⁶ No significant differences were seen between the baseline characteristics of the breakthrough EIB group, the non-breakthrough EIB group and the non-EIB group.

Individual characteristics of the breakthrough EIB group are shown in table 2. In this group, EIB occurred between 6 and 10 min of exercise (mean 7.75 min). Mean fall in FEV₁ 1 min after cessation of exercise was 34% from baseline (range 17–54%). Mean heart rate during exercise (calculated from the second minute of exercise) is shown in table 1. There is a significant difference in mean heart rate between the breakthrough EIB group and the non-EIB group (75.7±2.8% vs 79.5±2.9%, p<0.01; 95% CI 1.0% to 6.5%).

The pattern observed in most of the children in the breakthrough EIB group was an initial increase in FEV₁ during the first minutes of exercise. After a short plateau, FEV₁ progressively decreased, followed by a steeper fall in FEV₁ after exercise, as shown in figure 1. Figure 2 shows FEV₁ values during exercise in the non-breakthrough EIB group. After an initial increase in FEV₁, most children showed a slow decline in FEV₁ during the exercise challenge. Mean fall in FEV₁ 1 min after cessation of exercise was 21% from baseline (range 17–34%).

DISCUSSION

The main result of this study is that in the majority of children with EIB (ie, 12 out of 19) bronchoconstriction starts during submaximal exercise in cold air.

To our knowledge this study is the first to evaluate pulmonary function, as measured by FEV₁, during an exercise challenge in cold air in children with asthma. Several studies have described bronchoconstriction in adults with asthma during and after exercise. Rundell *et al* investigated EIB during exercise in cold air. They found that bronchoconstriction (defined as a fall >10% in FEV₁) occurs in adult athletes during prolonged exercise (~42 min) at 90–100% of maximum heart rate.¹⁰ Beck and Suman *et al* studied pulmonary function (FEV₁) in adults with asthma during different prolonged exercise protocols in laboratory settings and both observed bronchoconstriction during exercise after about 15 min of exercise.^{2 6 8 9} A few studies measured peak expiratory flow rate (PEFR) during exercise in children with asthma and reported that in up to 51.7% of children with asthma PEFR falls below the prechallenge value at the end of a 6–8 min exercise challenge, suggesting that EIB occurs frequently during exercise.^{17–19}

The mechanism of bronchoconstriction during exercise could be an imbalance between bronchodilator and bronchoconstrictor influences. During exercise, hyperpnoea causes drying and hyperosmolarity of the respiratory mucosa, leading to the release of inflammatory mediators and subsequent bronchoconstriction.⁴ Simultaneously, exercise has a bronchodilating potential, caused by the release of nitric oxide and prostaglandin PGE₂ and increased mechanical stretching of the airway smooth muscle through deep inspirations.⁶ Studies in adults with asthma describe a pattern of initial bronchodilation during exercise. After achieving a steady state for about 15 min, the constrictor stimulus prevails, with additional constriction after exercise.^{2 6 7 9 11} We observed the same pattern in children with asthma, however the timing of the events is markedly faster than in adults. The bronchodilator effect of exercise is transient in children and is rapidly followed by bronchoconstriction within minutes. This fast pattern may be

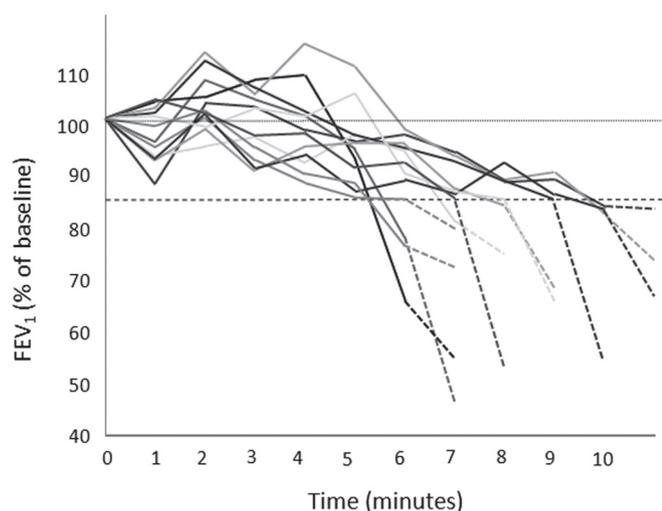


Figure 1 Response of FEV₁ during exercise in the breakthrough exercise-induced bronchoconstriction group. Dotted line: FEV₁ after exercise. FEV₁, forced expiratory volume in 1 s.

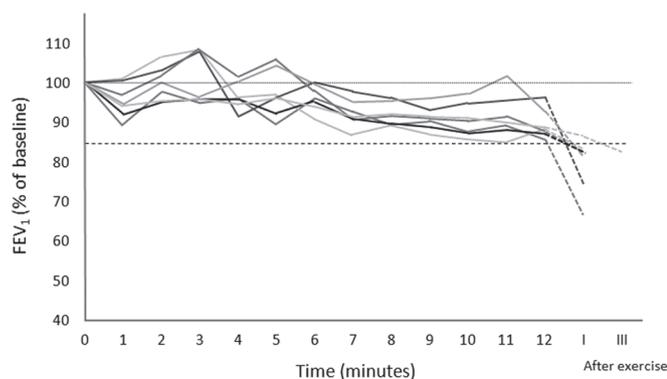


Figure 2 Response of FEV₁ during exercise in the non-breakthrough exercise-induced bronchoconstriction group. Dotted line: FEV₁ after exercise. FEV₁, forced expiratory volume in 1 s.

due to the twitchiness of young airways. The contribution of muscle spasm in the mechanism of EIB in children with asthma may be relatively high compared to that in adults. This would also explain children's quick recovery of pulmonary function after maximal bronchoconstriction.¹² Another explanation for EIB during exercise in children may be a failure of bronchodilator influences to counterbalance the bronchoconstrictor influences. Indeed, only two children were able to fully maintain their FEV₁ during exercise.

Our observation that EIB starts during a relatively short period of exercise in the majority of children with asthma implies that the thermal hypothesis to explain the pathophysiology of EIB cannot be sustained in children with asthma. According to this hypothesis, EIB is caused by rapid rewarming of the airways at the cessation of exercise induced hyperpnea.⁵ Anderson *et al*¹⁸ questioned this hypothesis in 1989 when they observed a fall in PEF_R in children with asthma during exercise.

Several remarks can be made about this study. Subjects performed an exercise challenge at approximately 80% of their maximum heart rate. According to the ATS guidelines for diagnosing EIB, the intensity of exercise should be set at a

heart rate of 80–90% of maximum. Testing at a relatively low exercise intensity probably underestimates the prevalence and severity of EIB.^{13–20} We deliberately chose an exercise intensity of 80% of maximum heart rate, since spirometry is easier to perform and a prolonged test easier to sustain during submaximal exercise. Retrospectively, mean heart rate during exercise was significantly lower in the breakthrough EIB group compared to the non-EIB group (75.7% vs 79.5%). We considered this difference was clinically irrelevant and did not cause breakthrough EIB (heart rate was even slightly lower in the breakthrough EIB group). Although we successfully titrated the intensity of exercise to approximately 80% of the predicted maximum heart rate in all children, the duration of exercise in the non-EIB group was longer and heart rate increased steadily during exercise, explaining the difference in mean heart rate.

Another comment can be made about the duration of the exercise test, which differs from regular exercise tests. Given that there is initial bronchodilatation during the first few minutes of exercise, a standardised protocol of 6 min could be too short to document a significant fall in FEV₁ during exercise.^{3–7} Therefore, we chose a 12 min exercise protocol, as most children show a rapid fall in FEV₁ directly after a regular exercise challenge of 6–8 min. Also, a submaximal prolonged test mimics real life exercise during play and sports. Indeed, we observed EIB in the majority of children during these 12 min. Moreover, the average time for EIB to occur was after 7.75 min of exercise. If EIB had been defined as a fall in FEV₁ >10% from baseline, instead of >15%, five more children would have had a positive breakthrough test (ie, 17 out of 19).¹³

One could argue that the observed fall in FEV₁ during exercise is a result of submaximal effort or respiratory muscle fatigue. However, all children performed technically adequate flow volume curves during exercise, irrespective of whether or not there was a fall in FEV₁.

Eleven children did not show EIB. This might be due to the fact that self-reported exercise induced symptoms are not always caused by EIB.^{21–22} Furthermore, we measured FEV₁ to a maximum of 5 min after exercise, which may underestimate the incidence of EIB as the time to maximal bronchoconstriction after exercise is between 2 and 12 min. However, the majority of children reach maximal bronchoconstriction in the first 5 min after exercise.¹²

The fact that bronchoconstriction can occur early during exercise in children with asthma is of clinical importance. Not only can it compromise the athletic performance of the child, but it can also influence a child's attitude to exercising. Dropping out during exercise lowers self-esteem and leads to avoidance of exercise and consequently cardiovascular deterioration.²³

Monitoring pulmonary function in children with asthma during exercise was feasible in our study and has benefits. It prevents the severe and uncontrolled falls in FEV₁ that can occur during and after a regular exercise challenge to measure EIB. Furthermore, a breakthrough test could potentially be used as a dose–response test, in which time to the occurrence of EIB can be considered as the degree of airway hyperresponsiveness.

In conclusion, measuring pulmonary function during exercise in children with asthma shows that the bronchoprotective effect of exercise is short-lived in children and that EIB frequently starts during, and not after, submaximal exercise. Moreover, it may provide additional clinical information,

as breakthrough EIB can seriously hinder participation in sports and active play and indicates uncontrolled asthma, for which appropriate therapy measures are needed. More research is needed to characterise children with asthma who are susceptible to airway obstruction during exercise and the influence of medication on this phenomenon.

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Competing interests None.

Ethics approval This study was conducted with the approval of the Medisch Ethische Toetsingscommissie Medisch Spectrum Twente, Enschede.

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REFERENCES

1. **Merikallio VJ**, Mustalahti K, Remes ST, *et al*. Comparison of quality of life between asthmatic and healthy school children. *Pediatr Allergy Immunol* 2005;**16**:332–40.
2. **Suman OE**, Beck KC, Babcock MA, *et al*. Airway obstruction during exercise and isocapnic hyperventilation in asthmatic subjects. *J Appl Physiol* 1999;**87**:1107–13.
3. **Stirling DR**, Cotton DJ, Graham BL, *et al*. Characteristics of airway tone during exercise in patients with asthma. *J Appl Physiol* 1983;**54**:934–42.
4. **Anderson SD**. How does exercise cause asthma attacks? *Curr Opin Allergy Clin Immunol* 2006;**6**:37–42.
5. **McFadden ER Jr**. Hypothesis: exercise-induced asthma as a vascular phenomenon. *Lancet* 1990;**335**:880–3.
6. **Beck KC**. Control of airway function during and after exercise in asthmatics. *Med Sci Sports Exerc* 1999;**31**:S4–11.
7. **Gotshall RW**. Airway response during exercise and hyperpnoea in non-asthmatic and asthmatic individuals. *Sports Med* 2006;**36**:513–27.
8. **Beck KC**, Offord KP, Scanlon PD. Bronchoconstriction occurring during exercise in asthmatic subjects. *Am J Respir Crit Care Med* 1994;**149**:352–7.
9. **Suman OE**, Babcock MA, Pegelow DF, *et al*. Airway obstruction during exercise in asthma. *Am J Respir Crit Care Med* 1995;**152**:24–31.
10. **Rundell KW**, Spiering BA, Judelson DA, *et al*. Bronchoconstriction during cross-country skiing: is there really a refractory period? *Med Sci Sports Exerc* 2003;**35**:18–26.
11. **Milanese M**, Saporiti R, Bartolini S, *et al*. Bronchodilator effects of exercise hyperpnea and albuterol in mild-to-moderate asthma. *J Appl Physiol* 2009;**107**:494–9.
12. **Vilozni D**, Szeinberg A, Barak A, *et al*. The relation between age and time to maximal bronchoconstriction following exercise in children. *Respir Med* 2009;**103**:1456–60.
13. **Crapo RO**, Casaburi R, Coates AL, *et al*. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000;**161**:309–29.
14. **Miller MR**, Hankinson J, Brusasco V, *et al*.; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J* 2005;**26**:319–38.
15. **Eggleston PA**, Guarrant JL. A standardized method of evaluating exercise-induced asthma. *J Allergy Clin Immunol* 1976;**58**:414–25.
16. **Cole TJ**, Bellizzi MC, Flegal KM, *et al*. Establishing a standard definition for child overweight and obesity worldwide: international survey. *BMJ* 2000;**320**:1240–3.
17. **Godfrey S**, Silverman M, Anderson SD. Problems of interpreting exercise-induced asthma. *J Allergy Clin Immunol* 1973;**52**:199–209.
18. **Anderson SD**, Daviskas E, Smith CM. Exercise-induced asthma: a difference in opinion regarding the stimulus. *Allergy Proc* 1989;**10**:215–26.
19. **Anderson SD**, Silverman M, König P, *et al*. Exercise-induced asthma. *Br J Dis Chest* 1975;**69**:1–39.
20. **Carlsen KH**, Engh G, Mørk M. Exercise-induced bronchoconstriction depends on exercise load. *Respir Med* 2000;**94**:750–5.
21. **Seear M**, Wensley D, West N. How accurate is the diagnosis of exercise induced asthma among Vancouver schoolchildren? *Arch Dis Child* 2005;**90**:898–902.
22. **Abu-Hasan M**, Tannous B, Weinberger M. Exercise-induced dyspnea in children and adolescents: if not asthma then what? *Ann Allergy Asthma Immunol* 2005;**94**:366–71.
23. **Vahlkvist S**, Inman MD, Pedersen S. Effect of asthma treatment on fitness, daily activity and body composition in children with asthma. *Allergy* 2010;**65**:1464–71.



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