

Exercise-induced bronchospasm, asthma control, and obesity

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ABSTRACT

Exercise-induced bronchospasm (EIB) commonly affects patients with asthma. However, the relationship between EIB and asthma control remains unclear. Exercise limitation due to asthma might lead to reduced physical activity, but little information is available regarding obesity and EIB in asthma. A recent survey evaluated the frequency of EIB and exercise-related respiratory symptoms in a large number of patients with asthma. The survey results were reanalyzed to address any relationship between EIB and asthma control and obesity. A nationwide random sample of children aged 4–12 years ($n = 250$), adolescents aged 13–17 years ($n = 266$), and adults aged ≥ 18 years ($n = 1001$) with asthma were interviewed by telephone. Questions in the survey addressed asthma symptoms in general, medication use, and height and weight. Asthma control was categorized using established methods in the Expert Panel Report 3. Body mass index (BMI) was calculated using standard nomograms and obesity was defined as a BMI ≥ 30 kg/m². Most children (77.6%), adolescents (71.1%), and adults (83.1%) had either “not well” or “very poorly” controlled asthma. Children with “not well” controlled asthma reported a history of EIB significantly more often than those with “well” controlled asthma. Asthma patients of all ages who had “not well” and “very poorly” controlled asthma described multiple (four or more) exercise-related respiratory symptoms significantly more often than those with “well-controlled” asthma. Obesity was significantly more common in adolescents with “not well” and “very poorly” controlled asthma and adults with “very poorly” controlled asthma. Children, adolescents, and adults with asthma infrequently have well-controlled disease. A history of EIB and exercise-related respiratory symptoms occur more commonly in patients with not well and very poorly controlled asthma. Obesity was found more often in adolescents and adults, but not children, with asthma, which was not well and very poorly controlled.

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Exercise-induced bronchospasm (EIB) has been estimated to affect up to 90% of asthma patients,^{1–6} but this estimate is based on limited data.⁶ The EIB Landmark Survey was, to our knowledge, the first effort to evaluate the frequency of EIB in a large number of asthma patients.^{7,8} In that nationwide survey of

randomly selected asthma patients, the reporting rates of EIB varied from 16.3% in children aged 4–12 years to 33.9% in adolescents aged 13–17 years, with 22.8% of adults reporting a history of EIB. Respiratory symptoms with exercise were more frequently reported than a history of EIB. Asthma patients noted that respiratory symptoms frequently interfered with their ability to participate in sports, outdoor activities, and even normal physical activity.

The EIB Landmark Survey provides the opportunity to address two other issues of clinical concern. First, respiratory symptoms during exercise are often considered a reflection of poor asthma control. EIB is thought to be more common in patients with more severe or poorly controlled asthma.⁶ However, information on the relationship between EIB, exercise-related respiratory symptoms and asthma control is limited. Second, many adolescents and adults in the United States perform insufficient physical activity on a regular basis to maintain good health.^{9,10} Reduced exercise is a concern regarding the development of obesity. Consequently, asthma patients with EIB or multiple exercise-related respiratory symptoms and reduced physical activity might more likely be obese. The objective of this study was to reanalyze the results of the EIB Landmark Survey and to evaluate the relationship between asthma control, determined using the Expert Panel Report 3 (EPR 3)¹¹ recom-

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mended methods, and a diagnosis of EIB, patient reported exercise-related respiratory symptoms, and obesity.

METHODS

Survey Population

The EIB Landmark Survey consisted of multiple parts, each conducted using telephone interviews in December 2009 and January 2010. There was a survey of EIB in the general public, a survey of EIB in children and adolescents with asthma, a separate survey of EIB in adults with asthma, and a survey of physicians caring for asthma patients. Only the portions dealing with the EIB survey in children, adolescents, and adults with asthma are reported. Patients with asthma were identified by randomly contacting 22,137 households in the United States. Of these households, 11,665 agreed to be screened for inclusion of one or more persons with asthma. Current asthma patients were defined as persons diagnosed with asthma and having experienced an asthma attack or asthma symptoms within the past year or currently taking medication for their asthma. In households with more than one eligible patient, the computer-assisted telephone interviewing system randomly selected one person by age as the designated patient. If the designated patient was between 4 and 17 years of age, the adult most knowledgeable about that patient's asthma and its treatment was interviewed. The surveys were conducted by the National Public Research Organization Abt SRBI, Inc., in partnership with Strategic Pharma Solutions, LLC. Teva Respiratory, LLC, sponsored the survey. Survey participants were guaranteed confidentiality. Interviews were only conducted after participants consented to participate by a verbal informed consent approved by an appropriate ethics committee.

Questionnaires

The EIB Landmark Survey included 84 questions developed by a faculty of primary care and asthma health care providers. The questions addressed demographics and baseline characteristics, asthma medication use, and height and weight. The survey respondents were specifically asked, "Has a doctor or other health care professional ever told you that you had exercise-induced asthma or exercise-induced bronchospasm?" The response to this question was used as the basis for determining whether there was a history of EIB. There were a series of questions that separately addressed the occurrence of exercise-related respiratory symptoms (shortness of breath, wheeze, cough, difficulty taking a deep breath, noisy breathing, and chest tightness) with activities. The number of these symptoms reported by survey respondents was calculated. The survey used a short-term period (*i.e.*, the

previous 4 weeks) to evaluate asthma symptom burden and medication use. The survey also queried the need for emergency care for asthma exacerbations over the past 12 months.

Asthma Control

Asthma control was determined using the EPR 3 criteria (*i.e.*, impairment by the frequency of daytime symptoms, nighttime awakenings, short-acting inhaled β_2 -agonists use, and the degree of asthma-related limitation of normal activities reported over the prior 4 weeks; risk by acute health care use reported over the previous 12 months) using the most severe category for any individual feature (see Table E1 in the online supplement). Asthma control was categorized as "well," "not well," or "very poorly" controlled.

Data Analysis

Body mass index (BMI) was determined from patient-reported height and -weight using standard nomograms. Obesity was defined as a BMI ≥ 30 kg/m². Descriptive statistics of questionnaire responses were compiled by Abt SRBI, Inc. (New York, NY). Comparisons were made within age groups for "not well" and "very poorly" controlled against "well" controlled using the *t*-test. The maximum expected sampling error for a simple random sample of 1000 patients was $\pm 3.1\%$ at the 95% confidence level.

RESULTS

Subject Characteristics

Most of the children and adolescents with asthma were boys, but most of the adults with asthma were women (Table 1). The distribution of BMI revealed that very few children (6.4%) and adolescents (10.1%) were obese, but a much larger proportion of adults (44.0%) with asthma were obese. All three age groups infrequently reported a previous history of EIB with children having the lowest rate (16.6%), adolescents the highest rate (33.9%), and adults an intermediate rate (22.8%). Nasal allergies were reported commonly and to a similar extent among all three age groups. A minority of children (22.4%) and adolescents (19.9%) reported having another health condition, but a majority of adults described having another health condition (54.8%).

Use of controller medication over the 4 weeks before the survey was highest in the adults (53.1%), lowest in the adolescents (41.4%), and intermediate in the children (48.0%; see Table E2 in the online supplement). The most commonly reported controller medications varied by age group. Children most commonly were on a leukotriene modifier (27.6%) or an inhaled corticosteroid (ICS; 26.8%). Adolescents were most often on a leukotriene modifier (27.1%) or an ICS with long-

Table 1 Patient characteristics for children aged 4–12 yr (*n* = 250), adolescents aged 13–17 yr (*n* = 266), and adults aged ≥18 yr (*n* = 1001) who participated in the survey (number with percent in parentheses)

Characteristic	Children Aged 4–12 yr (<i>n</i> = 250)	Adolescents Aged 13–17 yr (<i>n</i> = 266)	Adults Aged ≥18 yr (<i>n</i> = 1001)
Gender			
Male	161 (64.4%)	150 (56.4%)	285 (28.5%)
Female	89 (35.6%)	116 (43.6%)	716 (71.5%)
Age (mean in yr)	9.0	15.1	48.2
BMI (kg/m ²)*			
<18.5	101 (46.3%)	42 (16.3%)	10 (1.1%)
18.5–24.9	86 (39.4%)	140 (54.3%)	250 (27.1%)
25–29.9	17 (7.8%)	50 (19.4%)	257 (27.8%)
≥30	14 (6.4%)	26 (10.1%)	407 (44.0%)
History of EIB diagnosis*			
Yes	34 (16.6%)	77 (33.9%)	228 (22.8%)
No	164 (80.0%)	145 (63.9%)	761 (76.0%)
Do not know	7 (3.4%)	5 (2.2%)	12 (1.2%)
Nasal allergies			
Yes	126 (50.4%)	139 (52.3%)	624 (62.3%)
No	119 (47.6%)	126 (47.4%)	365 (36.5%)
Do not know	5 (2.0%)	1 (0.4%)	12 (1.2%)
Other health conditions			
Yes	56 (22.4%)	53 (19.9%)	549 (54.8%)
No	194 (77.6%)	212 (79.7%)	444 (44.4%)
Do not know	0 (0%)	1 (0.4%)	8 (0.8%)

*Incomplete data capture.

BMI = body mass index; EIB = exercise-induced bronchospasm.

Table 2 Asthma control determined by EPR 3 criteria (no. with percent in parentheses)

Asthma Control	Children Aged 4–12 yr (<i>n</i> = 250)	Adolescents Aged 13–17 yr (<i>n</i> = 266)	Adults Aged ≥18 yr (<i>n</i> = 1001)
Well controlled	56 (22.4%)	77 (28.9%)	169 (16.9%)
Not well controlled	138 (55.2%)	130 (48.9%)	468 (46.8%)
Very poorly controlled	56 (22.4%)	59 (22.2%)	364 (36.4%)

EPR 3 = Expert Panel Report 3.

acting inhaled β_2 -agonist combination product (21.4%). Adults most often reported taking an ICS + long-acting inhaled β_2 -agonist combination product (36.3%).

Only a small proportion of children (22.4%), adolescents (28.9%), and adults (16.9%) were categorized as having well-controlled asthma (Table 2).

EIB and Asthma Control

A history of EIB was reported significantly more often ($p < 0.05$) in children with not well-controlled asthma than in those with well-controlled asthma (Fig. 1). Although there was a higher reporting rate of a history of EIB in adolescents and adults with not well and very poorly controlled asthma than in those with well-controlled asthma, the differences were not significant. There

were more adolescents and adults described as having a previous diagnosis of EIB than children.

Exercise-Related Respiratory Symptoms and Asthma Control

Children, adolescents, and adults with not well and very poorly controlled asthma reported having four or more exercise-related respiratory symptoms significantly more often ($p < 0.01$) than those with well-controlled asthma (Fig. 2). The reporting rate of exercise-related respiratory symptoms was similar for each age group according to asthma control. Exercise-related respiratory symptoms were reported more often than a history of EIB.

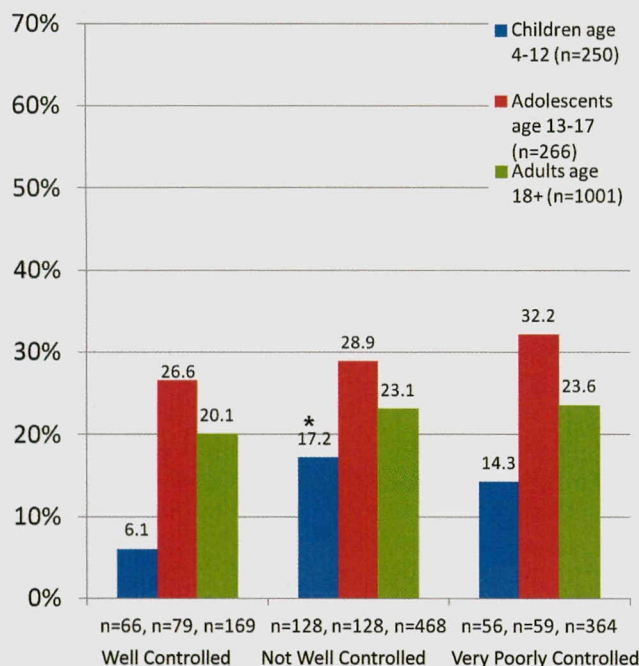


Figure 1. Percent of children aged 4–12 years, adolescents aged 13–17 years, and adults aged ≥18 years with a previous diagnosis of exercise-induced bronchospasm (EIB) by Expert Panel Report 3 (EPR 3) asthma control classification (* $p < 0.05$ versus well controlled).

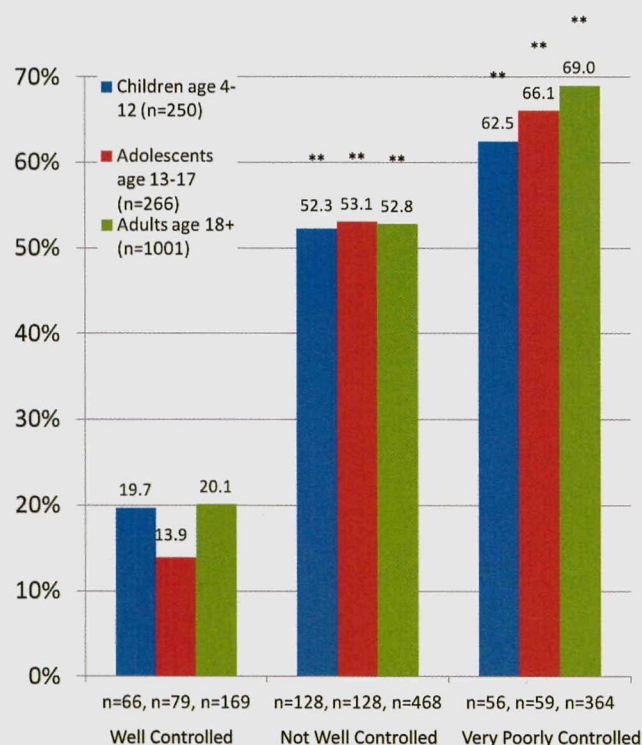


Figure 2. Percent of children aged 4–12 years, adolescents aged 13–17 years, and adults aged ≥18 years reporting four or more respiratory symptoms with exercise by Expert Panel Report 3 (EPR 3) asthma control classification (** $p < 0.01$ versus well controlled).

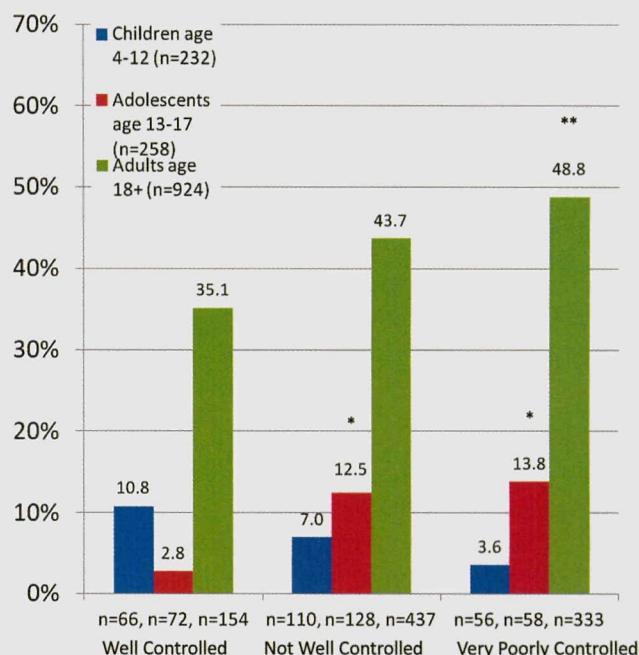


Figure 3. Percent of children aged 4–12 years, adolescents aged 13–17 years, and adults aged ≥18 years with obesity (body mass index [BMI], ≥30 kg/m²) by Expert Panel Report 3 (EPR 3) asthma control classification (* $p < 0.05$ versus well controlled, ** $p < 0.01$ versus well controlled).

Obesity and Asthma Control

The rates of obesity in children with not well and very poorly controlled asthma were not different from those with well-controlled asthma (Fig. 3). However, adolescents with not well and very poorly controlled asthma were significantly more likely ($p < 0.05$) to be obese than those with well-controlled asthma. Adults with very poorly controlled asthma were significantly more likely ($p < 0.01$) to be obese than those with well-controlled asthma. There was a trend ($p = 0.06$) for adults with not well-controlled asthma to be more obese than adults with well-controlled asthma.

DISCUSSION

This reanalysis of the EIB Landmark Survey confirms that a large proportion of this broad sample of children, adolescents, and adults with asthma living in the United States in 2009–2010 did not have a level of asthma control that met national treatment targets set in the EPR 3. Two other important observations can be made. First, a history of EIB and reporting of respiratory symptoms with exercise were more common in patients with not well and very poorly controlled asthma. Second, obesity was more common in adolescents and adults, but not children, with not well and very poorly controlled asthma than with well-controlled asthma.

The finding that most asthma patients in this survey, including children, adolescents, and adults, had not

well or very poorly controlled disease should not be surprising. Multiple surveys, using either telephone interviews^{12–16} or questionnaires,^{17–26} have shown that most patients with asthma are regularly symptomatic. The percent of patients with not well and very poorly controlled asthma found in this analysis of the EIB Landmark Survey is in the same range as noted in other studies. In a long-term, randomized, controlled study that used a similar definition of control based on the EPR 3, only ~10% of the asthma patients were categorized as well controlled during run-in.²⁷ The CHOICE survey, which used a similar approach to categorize asthma control, showed that only 14.3% of asthma patients on controllers had well-controlled disease.²⁸

Fewer asthma patients in this survey reported a history of EIB than previously estimated. The highest reporting rate of a previous history of EIB was found in adolescents at 33.9%. This is substantially below commonly cited estimates of up to 90% of asthma patients being affected by EIB.^{1–6} However, 78.8% of children and adolescents⁷ and 83% of adults⁸ reported at least one respiratory symptom with exercise, and a substantial percent described having four or more of these symptoms with exercise. This disparity between symptom reporting and an EIB diagnosis probably reflects limited recognition and diagnosis of EIB by health care providers. There is important clinical value to establishing the diagnosis of EIB because EIB symptoms can generally be effectively managed with short-acting inhaled β_2 -agonists¹¹ with the addition of appropriate additional controller medications as indicated. This reanalysis confirms the clinical suspicion that patients with not well and very poorly controlled asthma more often had a history of EIB and described four or more respiratory symptoms with exercise than patients with well-controlled asthma. This finding further emphasizes the need for improved asthma control.

Obesity is an epidemic in the United States. The prevalence of obesity in children and adolescents in the U.S. general population was 16.9% in 2009–2010²⁹ and in adults the prevalence was just over 35%.³⁰ In this analysis the rates of obesity for children and adolescents with asthma were lower than these national averages, but the rate of obesity in adults with asthma was higher. When rates of obesity were categorized by asthma control, they were found to be higher in adolescents and adults with not well and very poorly controlled asthma but, surprisingly, tended to be lower in children with not well and very poorly controlled asthma. Balfour-Lynn made a similar observation.³¹ In a long-term survey of children with chronic perennial asthma, “children most severely affected by the disease ...tended to be underweight” and teens tended to gain “an excessive amount of weight.”

The relationship between obesity and asthma is complex and controversial. Obesity is thought to be a risk

factor for asthma, but the mechanism of this interaction is not clear.³² The results of this analysis raise two different issues. Could uncontrolled asthma reduce the likelihood of obesity in children? Could avoidance of physical activity by children with uncontrolled asthma patients due to frustration with exercise-induced respiratory symptoms then contribute to the development of obesity in adolescents and adults? These are important issues because Vahlkvist and colleagues have shown in children that poorly controlled asthma is associated with reduced physical activity.³³ Improvement in asthma control in these children resulted in an increase in physical activity. Future studies are needed to determine whether reduced physical activity due to exercise-related respiratory symptoms in children with not well or very poorly controlled asthma could contribute to the development of obesity in adolescents and adults with asthma. Improving asthma control in children might help break this cycle of inactivity leading to later obesity.

There are limitations to a telephone survey. Because all information is self-reported, responder bias and inaccurate recall must be considered. This is of particular concern for the use of self-reported height and weight. However, previous work reassures us that self-reported height and weight are reasonably reliable when compared with directly measured values. Kuczmarski *et al.* found that there was a high correlation between self-reported height and weight and directly measured height and weight in young adults participating in the Third National Health and Nutrition Examination Survey.³⁴ In adults >60 years old, self-reported height tended to be lower than directly measured height, but the difference had only a small effect on calculated BMI. Sherry and colleagues reported that adolescent girls tended to underreport weight but that there was only a minimal effect on calculated BMI in adolescents when self-reported height and weight were used rather than directly measured values.³⁵ It should be noted that our definition of obesity was based on a BMI ≥ 30 kg/m². This is a standard definition for adults and adolescents, but in children an alternative definition based on BMI greater than the 99th percentile of a specified reference population has been recommended.³⁶ Recent work has shown that the adult definition of a BMI ≥ 30 kg/m² for children provides similar results as the proposed child definition.²⁹ For simplicity and ease of interpretation of results, we used the same obesity definition for all age groups. An asthma diagnosis was also based on patient self-reporting, but asthma may be misdiagnosed in obese patients.^{37,38} The likelihood of an asthma misdiagnosis in this survey was reduced by the requirement that patients either had a recent attack or were on asthma medications. Self-reporting of EIB is also a concern, because exercise-related symptoms are nei-

ther a sensitive nor specific indicator of EIB.⁵ In this study, the diagnosis of EIB was not established by survey responses. Instead, the patients were directly asked whether they had ever been told by a doctor or health care professional that they had exercise-induced asthma or EIB. The responder population was not re-balanced. Although this approach may have led to a sample not entirely representative of the U.S. population, it did allow for comparisons among groups within the responder sample. The EPR 3 recommends using spirometry results for control categorization but obtaining this information in a telephone survey was not feasible. Because this was a pilot analysis of previously collected data, prospective studies are urgently needed to further explore the issues raised.

In summary, the "EIB in Asthma" survey raises several important issues. National efforts must continue to emphasize the need for effective asthma control. EIB is probably an important, underrecognized component of not well and very poorly controlled asthma. This is clinically important because EIB, if appropriately diagnosed, can be effectively treated. Physical activity should be encouraged in patients with asthma for good general health. Asthma control should be achieved so that asthma patients can actively participate in any activity without limitations. Finally, the relationship between exercise-related respiratory symptoms in children and subsequent development of obesity in adolescents and adults with asthma warrants further evaluation.

Key Messages

- The 77.6% of children, 71.1% of adolescents, and 83.1% of adults with asthma were not well or very poorly controlled.
- A history of EIB and report of four or more respiratory symptoms with exercise were more common in patients with not well and very poorly controlled asthma.
- Obesity was more common in adolescents and adults, but not children, with not well and very poorly controlled asthma.

Capsule Summary

This article is relevant to practicing physicians and asthma specialists because it shows that respiratory symptoms with exercise are common in patients with not well and very poorly controlled asthma and that obesity occurs more often in adolescents and adults with not well and very poorly controlled asthma.

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