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Does exercise-induced bronchoconstriction affect physical activity patterns in asthmatic children?

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Abstract

Exercise-induced bronchoconstriction (EIB) is a sign of uncontrolled childhood asthma and classically occurs after exercise. Recent research shows that EIB frequently starts during exercise, called breakthrough-EIB (BT-EIB). It is unknown whether this more severe type of EIB forces children to adapt their physical activity (PA) pattern in daily life. Therefore, this pilot study aims to investigate daily life PA (amount, intensity, duration, and distribution) in children with BT-EIB, 'classic' EIB, and without EIB. A Fitbit Zip activity tracker was used for one week to objectively measure daily life PA at one-minute intervals. Thirty asthmatic children participated. Children with BT-EIB were less physically active compared to children without EIB (respectively 7994 and 11,444 steps/day, $p = .02$). Children with BT-EIB showed less moderate-to-vigorous PA compared to the children without (respectively 117 and 170 minutes/day, $p = .02$). Children with EIB (both BT and classic) had significant shorter bouts of activity and a less stretched distribution of bout lengths compared to the non-EIB group (all $p < .05$). These results emphasize a marked association between EIB severity and PA patterns in daily life, stressing the need for a thorough clinical evaluation of exercise-induced symptoms in childhood asthma.

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Introduction

Exercise-induced bronchoconstriction (EIB) is a frequent (80–90% of individuals) and highly specific morbidity of childhood asthma that is associated with reduced quality of life and uncontrolled asthma (Gotshall, 2002; Merikallio et al., 2005). In asthma, exercise induces hyperpnoea, which provokes the airway mucosa, triggering the inflammation cascade, resulting in bronchoconstriction (Gotshall, 2002; van Leeuwen et al., 2011). EIB is classically defined as a 'post-exercise airway obstruction resulting in a fall of the forced expiratory volume in 1 second (FEV_1) compared to pre-exercise values' (Gotshall, 2002). Exercise itself is a powerful bronchodilator and can delay the fall of lung function until exercise ceased. However, van Leeuwen et al. (2011) showed that in childhood, asthma bronchoconstriction frequently (63%) occurs during exercise, which is called 'breakthrough'-EIB (BT-EIB). BT-EIB is thereby accompanied with an earlier and deeper fall in lung function and can be considered as a more severe form of EIB (van Leeuwen et al., 2011).

Physical activity (PA) is paramount for a child, as it induces the development of a healthy cardiorespiratory system and provides opportunities for self-expression, building self-confidence, social interaction, and integration (World Health Organization (WHO), 2015). Moreover, being physically active brings extra benefits to asthmatic children as it reduces airway inflammation (Mendes et al., 2011) and PA mediates the relation between asthma and obesity (Leinaar et al., 2016). Consequently, children who are physically active in daily life have a better quality of life emphasizing the importance of activity promotion and monitoring in children, especially for children with asthma (Wafa et al., 2016).

Usually, children do not voluntarily engage in sustained periods of constant moderate-to-vigorous PA (MVPA). Instead, children's PA is characterized by highly frequent bouts of intense activity of short-duration, interspersed by intervals of light or sedentary activity (Bailey et al., 1995; Berman et al., 1998; Corder et al., 2008). Consequently, the time to recover from an activity is limited. Children are able to cope with this pattern of activity, due to their dynamic and fast heart rate recovery time (Baraldi et al., 1991). In children with (BT-)EIB, this dynamic capacity of the cardiorespiratory system may be reduced as bronchoconstriction limits the pulmonary gas exchange (Muñoz et al., 2008). Therefore, it might be difficult for children with (BT-)EIB to keep up with the high-frequent activity of their peers (Tsai et al., 2012). Children with BT-EIB experience symptoms of their asthma during exercise, which may lead to an even greater risk of dropping out during PA. Moreover, the fear of inducing an asthma episode may withhold children with (BT-)EIB from full participation in PA (Tsai et al., 2012; Vahlkvist and Pedersen, 2009).

Most studies concerning asthma or EIB in children and PA did investigate the difference in PA patterns between asthmatics and healthy controls (Anthracopoulos et al., 2012; Eijkemans et al., 2008; Firrincieli et al., 2005; Sousa et al., 2014; Tsai et al., 2012; Vahlkvist and Pedersen, 2009; Vangeepuram et al., 2014). These studies are not conclusive on the exact influence of asthma on PA patterns in children. A recent review suggest that there is no difference in the PA of children with or without asthma (Cassim et al., 2016). A strength of this review is that only accelerometer-based activity data sets were included. However, the included studies used different methods to assess the control of asthma such as questionnaires, physician judgments, basic spirometry, or other criteria, all of which lack sensitivity and specificity to detect asthma or EIB severity in children compared to bronchoprovocation tests (Crapo et al., 2000; Madhuban et al., 2011). Research should therefore have explicit emphasis on the current standard of assessing asthma and EIB severity, which in the case of EIB is the exercise challenge test (ECT). Therefore, the aim of this pilot study is to compare objectively measured PA patterns (amount, intensity, duration, and distribution of PA per day) in children with BT-EIB, classic EIB, and without EIB assessed with an ECT.

Methods

Study design

The study is a prospective observational study in asthmatic children, with classic EIB, BT-EIB, or without EIB. Children with pediatrician-diagnosed asthma, who were scheduled for an ECT between January and November 2015, were approached to participate in the study. Previous research revealed that EIB in children usually starts during or shortly after exercise compromising their physically activity (van Leeuwen et al., 2011). Based on this knowledge and our clinical experience, we expected a large effect size of (BT-)EIB on PA in daily life. A priori analysis of variance (ANOVA) sample size calculation (three groups, $\alpha = .05$, power $= .95$, effect size $= .8$) resulted in a total sample size of 30 subjects. It was expected that the children would be distributed quite evenly among the three groups (BT-EIB, classic EIB, or non-EIB). The local ethics committee approved to analyze the activity levels of 30 children for a period of one week, as the study did not fall under the scope of the Medical Research Involving Human Subjects Act (WMO). All parents and participants provided their informed consent prior to the start of the study.

Subjects

Thirty children aged between 4 and 14 years with pediatrician-based asthma, of the Medisch Spectrum Twente hospital in Enschede (the Netherlands), were included in this study. The asthma diagnosis was confirmed by the pediatric pulmonologist assessing medical history, physical examination, and lung function testing, as described in the Global Initiative for Asthma guidelines (Bateman et al., 2008). All children are in school, which provides two hours of physical exercise a week. The children were categorized in one of three groups (BT-EIB, classic EIB, or non-EIB). Categorization in these asthma groups was based on timing and fall of lung function after the ECT (Godfrey et al., 1999). The ECT was performed in a climate chamber (10°C) with spirometry, according to the American Thoracic Society guidelines (Crapo et al., 2000). To prevent any influence of the pharmacological effect of inhalation medication on the ECT results, subjects were asked to hold their use of inhaled steroids and short acting bronchodilators from the evening before the ECT. When subjects were using inhaled corticosteroids (ICS) in combination with long-acting bronchodilators, it was held 48 hours before the ECT. Children with a fall from baseline of the forced expiratory volume in one second (FEV_1) $\geq 20\%$, at one minute after exercise, were placed in the BT-EIB group. Children who did not have a fall from baseline of $\geq 20\%$ at 1 minute after exercise, but did develop a maximal fall from baseline in $FEV_1 \geq 13\%$ in at least one of the later measurements ($t = 3$, $t = 6$, $t = 9$, $t = 12$ minutes), were included in the classic EIB group. Children with a maximal fall from baseline in $FEV_1 < 13\%$ were placed in the non-EIB group.

Exclusion criteria were other (chronic) conditions interfering with daily activity, such as psychomotor retardation, injuries, neuromuscular disorders, and chronic fatigue syndrome. Moreover, children with respiratory infections in the two months prior to planned ECT or oral steroid use in the two months prior to the planned ECT were excluded.

Measures

Demographic characteristics, such as age, body mass index (BMI) *z*-scores, gender, allergic rhinitis diagnosis, and medication use, were obtained from the electronic patient record. Baseline lung function (FEV_1% predicted) and the maximal fall in FEV_1 after exercise were obtained during the ECT.

PA was assessed using the Fitbit Zip wireless activity tracker (Fitbit Inc., San Francisco, CA). The subjects wore the activity tracker for five days from Monday to Friday in a representative school week, without (bank) holidays, reflecting the subjects' average habitual activities (Trost et al., 2012). This monitoring period took place prior to the ECT and both the subjects and pediatricians were blinded for the monitoring results to prevent any carry-over-effects. The subjects were instructed to attach the tracker at the hip and remove it only during bedtime and before activities involving water (such as showering or swimming). The screen of the tracker was taped off to prevent feedback on activity levels during the study period.

PA outcome measures were the amount of PA (total number of steps per day), PA intensity (number of minutes spent at each of four activity levels (inactive, light, moderate, and vigorous activity)), the average duration (bout length), and the distribution of activities from at least moderate intensity. This distribution is expressed as a number; the scale parameter of the Weibull distribution (Lehman, 1963). The Weibull scale parameter described the stretching of a distribution (decreasing amplitude and increasing width). In addition, self-reported symptoms were assessed with daily asthma control questionnaires. Subjects were asked to fill in the children questions of the Childhood Asthma Control Test (C-ACT) at the end of each measuring day.

Data analysis

Access to the Fitbit Partner API was requested and obtained in order to be able to download minute-to-minute data (using OAuth 2.0 authorization). Minute-to-minute data were analyzed with Matlab (MathWorks®, Released 2017, Version 2017a). Subjects with incomplete data sets (<80% of weartime) were excluded from analysis. Caloric expenditure data of Fitbit were converted to activity levels using the Metabolic Equivalents (MET). MET values of 1 (kcal/kg/hour) were seen as inactive, between 1 and 3 as light activity, between 3 and 6 as moderate activity, and larger than 6 as vigorous activity (Belcastro et al., 2012). Daily means were calculated for each of the activity parameters (amount of steps, minutes of activity in each intensity level, activity duration, and Weibull distribution scale parameter).

The answers to the child questions of C-ACT questionnaire were scored (0 to 3 for each question) in order to obtain a perception score of the daily symptoms of the children (Liu et al., 2007). Low C-ACT scores indicate more daily symptoms and high C-ACT scores indicate less symptoms. The C-ACT scores of each measuring day of all children were plotted versus the corresponding daily minutes of MVPA.

Table 1. Baseline characteristics.

	Asthma groups		
	Non-EIB ($n = 7$, 27%) Mean (SD)	Classic EIB ($n = 11$, 42%) Mean (SD)	BT-EIB ($n = 8$, 31%) Mean (SD)
Age (years)	10.0 (3.6)	8.1 (2.5)	11.1 (3.6)
BMI z-score[a]	0.42 (1.33)	−0.26 (1.20)	0.40 (1.24)
Gender (male/total)	0.71	0.73	0.88
Allergic rhinitis	6/7	9/11	7/8
ICS use	4/7	10/11	8/8[b]
ICS-LABA use	0/7	0/11	2/8[b,c]
Baseline FEV_1 (% predicted)	93.8% (10.0%)	85.0% (14.7%)	76.7% (16.5%)
Max FEV_1 fall at ECT	−3.7% (6.2%)	−20.7% (5.1%)[b]	−48.6% (9.9%)[b,c]

FEV_1: forced expiratory volume in one second; ECT: exercise challenge test; EIB: exercise-induced bronchoconstriction; BT-EIB: breakthrough-EIB; BMI: body mass index; ICS-LABA: Inhaled corticosteroids and long-acting beta(2)-agonist combination.
[a]Based on the WHO Multicentre Growth Reference Study Group (2006) (Onis de, 2008).
[b]*p* Values <0.05 compared to non-EIB.
[c]*p* Values <0.05 compared to classic EIB.

Statistical analysis

Descriptive statistics were used to examine the outcome measures and were expressed in means ($\pm$ standard deviation). Univariate analyses were performed with SPSS statistics (IBM Corp. Released 2013, Version 22.0) to test for significant differences of PA measures, EIB severity, and demographic variables between the asthma groups. Homogeneity of variances was verified with the Levene's test. The Shapiro–Wilks test was used to determine whether the variables were normally distributed among all asthma groups. The variables that did not have a normal distribution were tested with the nonparametric Kruskal–Wallis test followed by multiple comparisons. Normally distributed variables were tested with ANOVA followed by Dunnet's test for the post hoc comparisons of the three groups. *p* Values below or equal to .05 were considered as significantly different. A *p* value between .05 and .15 was considered as a trend. Cohen's effect sizes (d) were calculated to indicate the strength of the effect. Cohen classified effect sizes as small ($d = 0.2$), medium ($d = 0.5$), large ($d = 0.8$), and very large ($d \geq 1.3$).

Results

Three subjects were excluded due to an insufficient amount of wearing days (<80%) and one subject was excluded as the data of the Fitbit could not be obtained due to damage to the device. Of the remaining 26 children, 8 were placed in the 'BT-EIB group', 11 in the 'classic EIB' group, and 7 were classified as 'non-EIB'. Table 1 shows an overview of the baseline characteristics of these subjects. No significant differences in baseline characteristics were found.

Amount of activity—Average steps per day

Children with BT-EIB took significantly fewer steps per day (7994 $\pm$ 2200) compared to the children without EIB (11,444 $\pm$ 3348) ($p = .02$), which corresponds with a Cohen's effect size (d)

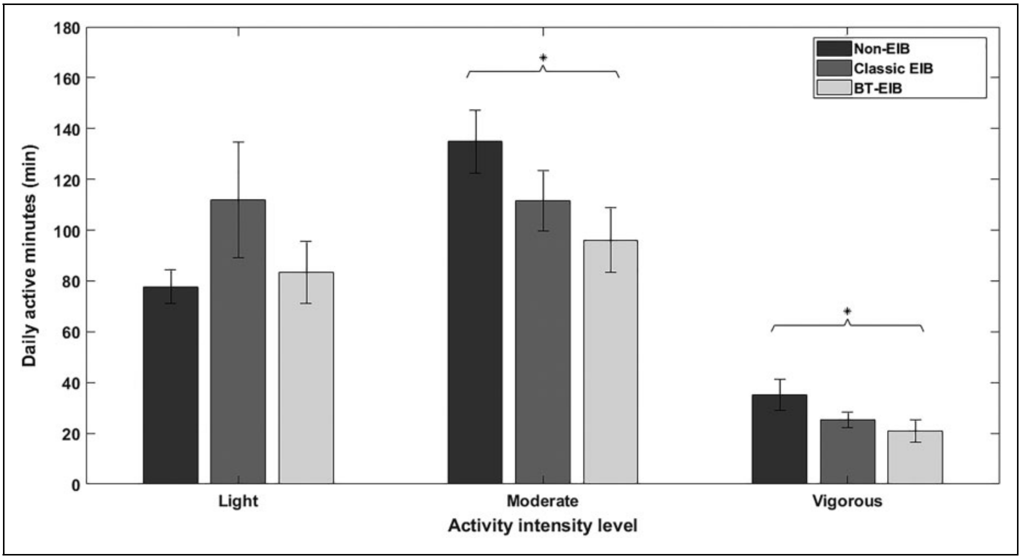

Figure 1. The average minutes spent in each activity intensity level per day. The error bars show the standard error. Significant differences ($p < .05$) are indicated with an asterisk (*).

of 1.22. There was a trend toward fewer steps in children with classic EIB (9048 $\pm$ 2627) compared to the children without EIB ($p = .07$, $d = 0.99$).

Activity intensity—Number of minutes spent in each activity level

Children with classic EIB (1191 $\pm$ 54) and without EIB (1192 $\pm$ 80) had a similar amount of inactive minutes per day. Children with BT-EIB (1240 $\pm$ 60) had more inactive minutes compared to children without EIB, however this differences was not significant ($p = .11$, $d = 1.03$).

Figure 1 shows the amount of active minutes in each activity type (light, moderate, and vigorous). The BT-EIB group showed fewer minutes of activity compared to children without EIB, predominantly consisting of less MVPA ($p = .02$, $d = 1.42$). The classic EIB group showed a trend toward less MVPA compared to children without EIB ($p = .09$, $d = 0.50$). Furthermore, a trend of a higher number of minutes spent in light activity was seen in children with classic EIB compared to children with BT-EIB and without EIB ($p = .15$).

Activity duration and distribution—Activity bout length

Figure 2 shows the average bout length and bout length distribution. In children with BT-EIB activities longer than 1 minute at or above moderate activity level lasted on average 2 minutes and 42 seconds ($\pm$21 seconds), for children with classic EIB 2 minutes and 48 seconds ($\pm$24 seconds) and for children without EIB 3 minutes and 26 seconds ($\pm$40 seconds). Both differences between the non-EIB group and the BT-EIB group ($p = .02$, $d = 1.39$) and between the non-EIB group and the classic EIB group ($p = .03$, $d = 1.16$) were significant.

The Weibull scale parameter was calculated to indicate the shape of the bout length distributions of all subjects (Figure 2). The non-EIB group showed an average scale parameter of 4.4E-3

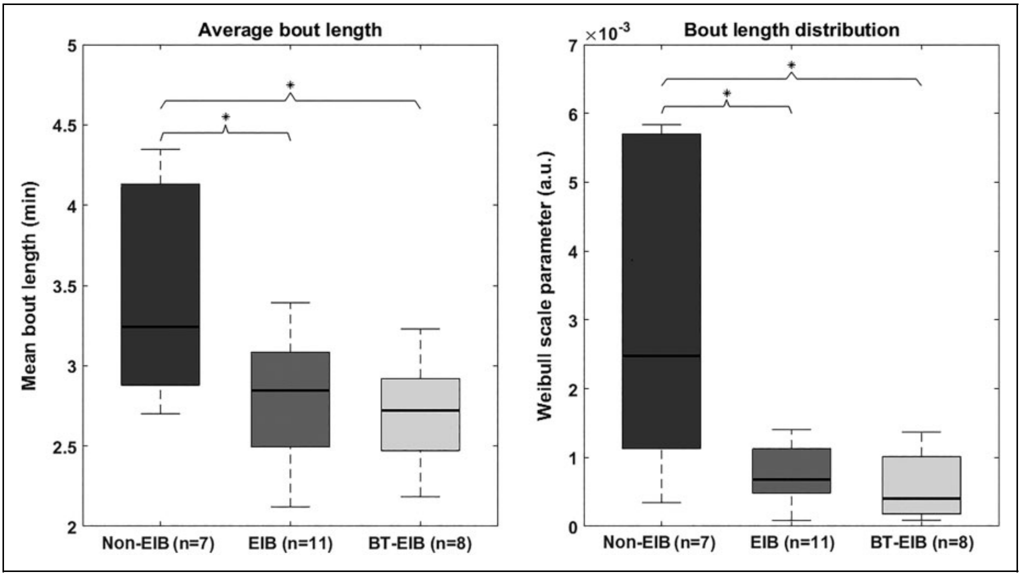

Figure 2. Boxplots of the average bout length (left) and the bout length distribution (right) between the different asthma groups. The boxplots display the median, interquartile ranges, and extreme values. Significant differences (p < .05) are indicated with an asterisk (*).

($\pm$1.8E-3), the EIB group a lower value of 1.1E-3 ($\pm$3.5E-4) ($p = .03$, $d = 0.93$), and the BT-EIB group showed an even lower mean value of 0.7E-3 ($\pm$2.7E-4) ($p = .01$, $d = 1.06$) compared to the non-EIB group.

Asthma symptoms versus MVPA

Sixty-nine percent (90/130) of the daily C-ACT questionnaires were filled in correctly. Figure 3 shows the C-ACT scores of each measuring day of all children versus the corresponding daily minutes of MVPA. As shown in Figure 3, C-ACT scores did not correlate in a linear fashion with MVPA (R^2 .01, $p = .47$). Rather, above a threshold C-ACT score of 7, there was no correlation at all with MVPA; in contrast, below the threshold C-ACT score of 7, a decrease in MVPA was seen with decreasing C-ACT scores, although this decrease was not clinically significant (R^2 .09, $p = .34$).

Discussion

This study showed that children showed that children with EIB have different activity patterns compared to children without EIB. Most striking are the children with BT-EIB, who underwent less activity and had shorter and less intense activity bouts compared to children without EIB. All these outcomes show large effect sizes (>.8). Although causality cannot be indicated, these large effect sizes suggest a strong relation of BT-EIB and the quality and quantity of PA in daily life in childhood asthma. This stresses the need for a thorough clinical evaluation of exercise-induced symptoms. Children with classic EIB also showed significantly shorter bouts of activity compared to the children without EIB, suggesting that the bout length might be a potential tool to predict EIB severity.

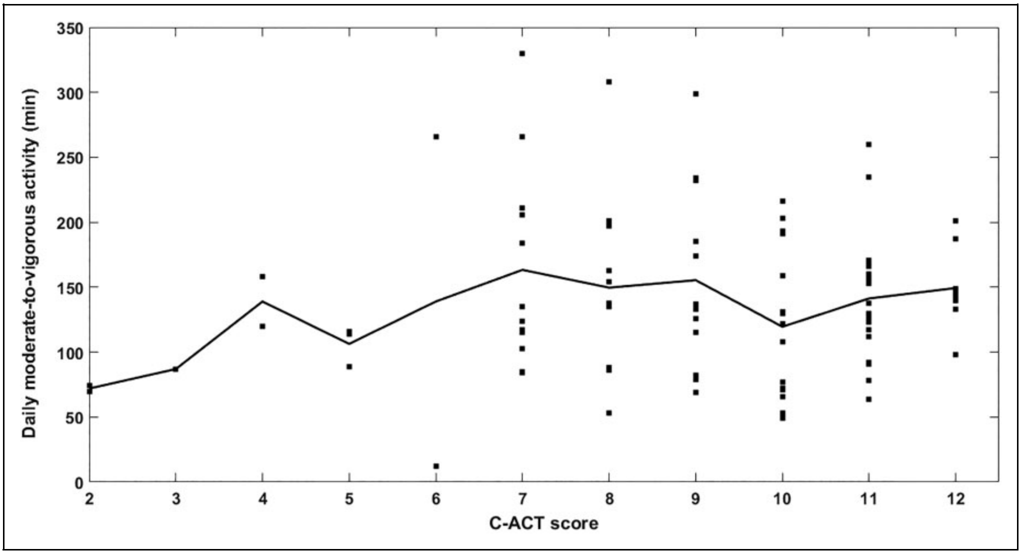

Figure 3. The minutes of daily MVPA versus the C-ACT symptom score. The bold line indicates the mean daily MVPA for each C-ACT symptom score. The horizontal dotted line indicates the average daily MVPA of children with a C-ACT score above 7, which corresponds with 150 minutes. The vertical dotted line indicates the critical bottom of the C-ACT score. A decrease in activity can be seen in days with lower C-ACT scores. MVPA: moderate-to-vigorous physical activity.

This is the first study that used both an ECT in a climate chamber to assess EIB severity and accelerometers to objectively measure activity patterns. Anthracopoulos et al. (2012) investigated the association between EIB and PA and assessed EIB by a standardized free running ECT. Their conclusion is in line with our results, as they revealed that decreased levels of PA, assessed with an activity questionnaire, are associated with EIB. Our study revealed that children with classic EIB have shorter bouts of activities and show a trend of less intense activities. Furthermore, they seem to compensate the lack of intense activities by performing more light activities. This compensation strategy could be a behavioral adaptation to prevent dropping out during PA with peers. In children with BT-EIB, this compensation mechanism was not found, which may indicate that these children could not compensate their limitation and were forced to drop out of PA. These findings imply that activity monitoring could therefore be very valuable in pediatric asthma care, as it provides pediatricians with objective information that may strengthen the decision for a step up in treatment to facilitate children with (BT-)EIB in full PA participation with peers. Besides, activity monitoring could provide children and parents with the awareness of their asthma induced change in activity patterns, which may offer opportunities for increased self-management.

PA recommendations for children

In this study, we observed that children with BT-EIB were significantly less active compared to children without EIB. Children without EIB took about 11,500 steps a day, which is just within the range (11,000–15,000) of healthy schoolchildren (Tudor-Locke et al., 2011). Children with classic EIB and BT-EIB took respectively 9000 and 8000 steps a day, revealing a lack of activity in children with (BT-)EIB.

International guidelines recommend a minimum of 60 minutes MVPA per day, but do not mention the exact proportion of vigorous PA (WHO, 2015). Vigorous intensity activities induce more improvement in cardiorespiratory fitness and bone and muscle strength (WHO, 2015). This study showed that on average children with BT-EIB are physically active for 95 minutes in moderate intensity level and 20 minutes in vigorous activity daily. Therefore, these children achieved the minimum recommended activity goal. However, children with BT-EIB still show significantly fewer intense activities compared to the non-EIB group. Furthermore, accelerometry does take all short burst activities into account, where the guidelines were established based on adding up longer lasting activities ($\pm$10 min or more) like walking, cycling and doing sports. This could underestimate the actual required MVPA measured with accelerometry. Therefore, it is advised that international guidelines should notice and explain the possible effect of the used PA assessment method on the PA outcome measures in children. We furthermore suggest supplementing recommendations on the specific amount or proportion of vigorous PA in children based on accelerometer data.

The relation of asthma symptoms and PA

The MVPA does not correlate with the C-ACT scores, indicating that the C-ACT questionnaire might not be a good predictor of activity limitation due to (BT-)EIB. Further research with a larger sample size and a longitudinal follow-up of the C-ACT and the PA patterns, including periods with high and low C-ACT scores, is needed to verify these results.

Strengths and limitations

This is the first study that used both an ECT in a climate chamber to classify EIB and accelerometers to measure activity patterns, both being the gold standard in their measurement domain for children (Corder et al., 2008; Crapo et al., 2000). This approach revealed significant differences in activity patterns, despite a limited number of participants, suggesting large effect sizes between PA and EIB. This research showed that throughout all parameters, almost all effect sizes were large to very large, indicating that daily activity patterns seem to be a quantifiable measure of EIB in asthmatic children. Still, future research should investigate our findings with larger sample sizes to either confirm or refute statistical significance.

The activity monitoring time frame might be a limitation in this study. Children in this study wore the activity tracker for five consecutive schooldays. Their daily schedule for that week might affected the number of steps taken or the type of PA they did. Trost et al. (2012) described that in children a monitoring time frame of five days is required to achieve a reliability coefficient of .80. To prevent further unreliability of possible confounding variables, it was chosen to set the monitoring period from Monday to Friday in a representative week, without (bank) holidays, reflecting the subjects' average habitual activities. A next step would be to use an activity tracker as part of treatment, and have long-term data, which can be used for trend analyses or multilevel analyses.

This study was limited by a relative small amount of days that children had low C-ACT scores. Throughout all measuring days in all children, only 10 days were registered with a C-ACT score below 7, which made testing the effect of symptom control on daily activity patterns unreliable. The results on this subject therefore remain inconclusive in this study. Follow-up research would be interesting as the experience of symptoms might be related to the daily activity patterns in children. In this case, during sample size calculation it should be taken into consideration that on average children with asthma indicate one out of nine days with a C-ACT score below 7.

Activity data of children need to be stored in small epoch lengths, as long epoch lengths are known to underestimate high intensity activities (Aibar and Chanal, 2015; Rowlands and Eston, 2007). Often used epoch lengths in monitoring activities of children are epochs smaller than 15 seconds (Anthracopoulos et al., 2012; Rowlands et al., 2009; Tulchin-Francis et al., 2014; Yiallouros et al., 2015). The Fitbit Zip was used to capture accelerometer data with an epoch length of one minute. Therefore, the Fitbit Zip might fall short in monitoring the exact characteristics of short burst activity in children. However, symptoms of BT-EIB do not arise in activities shorter than two minutes (van Leeuwen et al., 2011). So an epoch length of one minute should be sufficient for observing rough differences in the distribution of relevant activity lengths between children with (BT-)EIB and without EIB, as showed in this pilot study.

Conclusion

This study reveals a marked association between EIB severity and PA patterns in daily life, indicating the need for activity monitoring and thorough clinical evaluation of exercise-induced symptoms in childhood asthma care. This study also shows that both children with EIB and BT-EIB perform shorter activities, suggesting that the bout length and the bout length distribution might be a sensitive tool to predict EIB severity.

Author's note

MR van der Kamp is also affiliated with Roessingh Research and Development, Enschede, Netherlands.

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