Physical activity in young children is reduced with increasing bronchial responsiveness

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Background: Physical activity is essential for young children to develop adequately and for quality of life. It can be lower in children with subclinical asthma, and therefore methods to reveal subclinical reduction in physical activity in young children are warranted.

Objective: We sought to study an association between physical activity in preschool children and objectively assessed intermediary asthma phenotypes.

Methods: We studied 253 five-year-old children (127 girls) participating in the Copenhagen Prospective Studies on Asthma in Childhood. The main outcome measure was level of physical activity assessed objectively with accelerometers worn on an ankle for 4 weeks. Objective assessment of asthma intermediary phenotypes included prebronchodilator and postbronchodilator specific airway resistance, bronchial responsiveness to cold dry-air hyperventilation, and exhaled nitric oxide levels. Analyses were performed with generalized linear model and principal component analysis.

Results: Physical activity was inversely associated with bronchial responsiveness (relative rate, 0.89; 95% CI, 0.83-0.95; $P = .007$) and significantly increased in the months of spring and summer ($P < .001$) and in boys (relative rate, 1.16; 95% CI, 1.09-1.25; $P < .001$). Physical activity was independent of asthma diagnosis, age, body mass index, baseline specific airway resistance, reversibility to β_2-agonist, sensitization, and exhaled nitric oxide level.

Conclusion: Physical activity in preschool children was reduced with increasing bronchial responsiveness. The reduced physical activity was subclinical and not realized by parents or doctors despite daily diary cards and close clinical follow-up since birth. This observation warrants awareness of even very mild asthma symptoms in clinical practice. (J Allergy Clin Immunol 2010;125:1007-12.)

***Key words:** Accelerometer, physical activity, exercise, bronchial responsiveness, young children*

Children, particularly young children, experience and learn through physical activity and are often more dependent on physical ability than adults. Physical activity is essential to the young child for developing physical strength and dexterity and ensuring normal growth and good health. Recent studies have highlighted the health benefits of exercise, such as an improved quality of life and a decreased risk of becoming overweight.[1-4] Furthermore, less active children have been shown to cluster risk factors for cardiovascular disease.[5] Prospective studies in children[6] and in adult twins[7] have shown that the development of asthma was associated with decreased physical activity, although the direction of causality is unknown. Furthermore, asthmatic symptoms have been identified as a barrier to exercise by parents and children,[8] and a majority of children have reported that the worst thing about their asthma is their inability to participate in sports.[9]

Bronchodilator treatment as needed is recommended for symptoms of exercise-induced asthma for all age groups and asthma severities.[10] However, the success of this strategy assumes the child is able either to self-medicate or report symptoms. In young children this might not be feasible.

We have assessed physical activity objectively in 5–year-old children to examine whether intermediary asthma phenotypes would be reflected in the child's physical activity. Long-term physical activity was assessed with accelerometers. Lung function was evaluated based on prebronchodilator and postbronchodilator specific airway resistance (sRaw), bronchial responsiveness to cold dry-air hyperventilation, and exhaled nitric oxide levels. We hypothesized that exercise-induced symptoms would often go unnoticed and untreated, leading to subclinically reduced physical activity in proportion to asthma propensity.

This was a nested study within the prospective clinical birth cohort study the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC).[11-14] The COPSAC study provided the setting of children monitored closely and prospectively for signs of asthma since birth and included children with the full spectrum of asthma severities and wheezy disorders, as well as healthy children.

METHODS

Ethical approval

Oral and written informed consent were obtained from all parents of participating children. The study followed the guiding principles of the Declaration of Helsinki and was approved by the Ethics Committee for

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Abbreviations used
BMI: Body mass index
COPSAC: Copenhagen Prospective Studies on Asthma in Childhood
PCA: Principal component analysis
sRaw: Specific airway resistance

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Subjects

COPSAC is a cohort of 411 children born to mothers with asthma.[11-14] Children in this cohort were monitored with daily diaries for asthma symptoms and seen by the research doctors at 6-month intervals, as well as for any acute lung symptoms, at the asthma research center observant to and treating any asthma symptoms in accordance with a strict predefined algorithm. This ensured best practice for optimal symptom control and minimized the risk of overlooking even mild asthma. Standardized physical examination and history were obtained by the doctors at the research center, together with comprehensive objective assessments and lung function tests at the half-year visits. The COPSAC cohort has previously been described in detail.[11-14]

Physical activity assessment

The omnidirectional accelerometer Actical (Philips Respironics, Murrysville, Pa) was placed on the lateral side of the right or left ankle with a strap. The monitors were always oriented in the same direction. The Actical is sensitive in multiple planes to the acceleration of movements and generates an electric charge (a count with no unit) that is proportional to the applied acceleration. The parents and the child were instructed to leave it on day and night for 28 days, including during bathing. The strap was fixed with a cable tie to ensure compliance. Accelerometers were provided to the children consecutively as they visited the clinic for routine assessments. Epoch length was set to 1 minute.

Lung function tests

Lung function was measured by using whole-body plethysmography (Master Screen Body; Erich Jaeger, Stuttgart, Germany) to determine the sRaw.[15,16] Bronchial responsiveness was determined by hyperventilating −18 °C cold dry air. The test was done as a single-step isocapnic hyperventilation test lasting 4 minutes. The ventilation rate was aimed at 1 L/min/kg body weight.[17] A face mask fitted with a mouthpiece was used during measurement of sRaw and during hyperventilation. This ensured mouth breathing and prevented inhalation of room air. An animated computer program guided the child to maintain an adequate frequency of breathing.

Reversibility to bronchodilator was determined as the change in sRaw after inhalation of 2 doses of 0.25 mg of short-acting β_2-agonist (Terbutaline; AstraZeneca, Lund, Sweden) administered through a facemask and a nonelectrostatic spacer. The postmedication test was performed after 20 minutes.

Exhaled nitric oxide was measured (NIOX; Aerocrine, Stockholm, Sweden) in duplicates in accordance with international guidelines.[18] An animated computer program guided the child.

Any β_2-agonists were withheld 12 hours before the tests. In cases of acute respiratory tract infection, the tests were postponed for at least 2 weeks.

All tests were performed at scheduled visits and by the same experienced examiners.

Asthma diagnosis

Asthma was diagnosed by the doctor at the research unit according to international guidelines,[10] with the emphasis on a history of persistent symptoms recorded in diaries and in need of short-acting β_2-agonists, as previously described in detail.[11,12] Symptoms that were judged to be typical of asthma were exercise-induced symptoms, prolonged nocturnal cough, persistent cough outside the common cold, and symptoms causing wakening at night. Furthermore, the diagnosis required symptom improvement during a 3-month trial of inhaled corticosteroids and relapse when this medication was stopped.

Sensitization

Specific IgE levels were determined by using a screening method at age 6 years (ImmunoCAP, Phadiatop Infant; Pharmacia Diagnostics AB, Uppsala, Sweden) for IgE against the most common food and inhalant allergens. Phadiatop Infant values of 0.35 kU/L or greater were considered indicative of sensitization and were analyzed as a dichotomized end point.

Data analysis

Subjects with activity measurements lasting less than 7 days and days with a total of less than 20 hours were considered noncompliant and excluded from the analysis. Only lung function measurements performed within ±3 months of the activity test were included in the analysis. Children receiving oral or inhaled corticosteroids up to 30 days before a given test were analyzed as being on controller medication at the time of that test.

Bronchial responsiveness was analyzed as a continuous variable indicating the relative change in sRaw from baseline to the postchallenge test.

Minute-by-minute activity counts from the Actical monitor were compiled from 12:00 to 18:00 for the main analysis and from 09:00 to 12:00 and 08:00 to 20:00, respectively, for subanalyses.

We used the raw activity counts in the analyses.[19] Activity counts were analyzed by means of marginal log-linear Poisson regression, with log (number of minutes included in activity count) as offset. We used generalized estimating equation methods to account for within-child dependence. *P* values thus correspond to robust score tests and robust SEs were used to calculate 95% Wald CIs. The correlation structure assumed for the repeated measurements is the working independence correlation structure. An unadjusted analysis of association between physical activity and each of the variables studied was performed. This was done as a complete case analysis. Subsequently, we adjusted for the potential confounders of sex and month. Finally, we examined the importance of baseline lung function using forward selection.

Unpaired *t* tests and χ^2 tests were used for the drop-out analysis.

The daily activity profiles were also analyzed by means of principal component analysis (PCA).[20] The first principal components of PCA provide a summarized representation of the variations present in the data. The association between physical activity and asthma phenotypes was tested by using the Monte-Carlo permutation test.

Statistical analyses were performed with SAS software (version 9.1; SAS Institute, Inc, Cary, NC) and the R statistical software package (version 2.7.0), including the packages ade4 and vegan.[21]

RESULTS

Activity data were available for 253 (127 girls) of the 411 children of the COPSAC cohort (62%). The flow of subjects into the analysis is detailed in Fig 1. Characteristics of the participants included in the analysis are outlined in Table I. There was no sex difference in age ($P = .80$), body mass index (BMI; $P = .71$), days recorded ($P = .64$), diagnosis of asthma ($P = .13$), or bronchial responsiveness ($P = .82$).

The accelerometer was worn for an average of 26 days (range, 7-28 days). The highest activity was from 12:00-18:00, and this period was therefore chosen for the primary analysis. There was a significant variation during the year, with children being more active in the spring and summer months compared with the winter months ($P < .001$). Boys were more active than girls (relative rate, 1.16; 95% CI, 1.09-1.25; $P < .001$). Age, BMI,

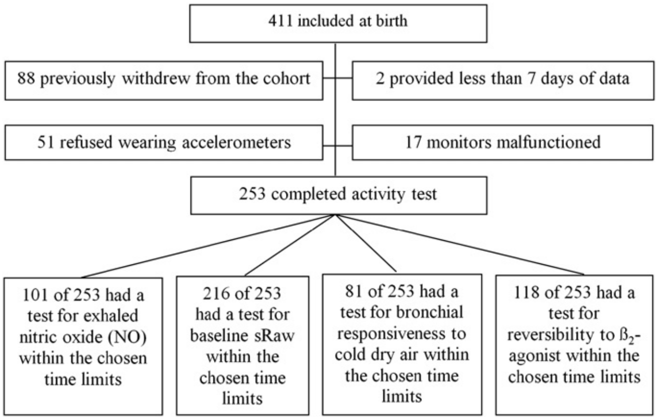

FIG 1. Flowchart of patient participation and numbers of children who have completed a given lung function test.

rhinitis, sensitization, and socioeconomic factors (household income, mother's occupation, and mother's education) were not associated with physical activity.

Physical activity was inversely associated with bronchial responsiveness (Fig 2; adjusted relative rate, 0.89; 95% CI, 0.83-0.95; P = .007): the calculations have been performed so that the relative rate indicates the change in activity corresponding to a 20% increase in bronchial responsiveness. The association remained statistically significant when analyzed for the periods 09:00-12:00 (adjusted relative rate, 0.90; 95% CI, 0.84-0.97; P = .02) and 08:00-20:00 (adjusted relative rate, 0.90; 95% CI, 0.84-0.96; P = .01), when stratified for sex (boys: adjusted relative rate, 0.88; 95% CI, 0.79-0.97; P = .04; girls: adjusted relative rate, 0.90; 95% CI, 0.85-0.97; P = .01), and when a subgroup analysis was performed on nonasthmatic subjects only (adjusted relative rate, 0.90; 95% CI, 0.82-0.98; P = .03). Bronchial responsiveness, sex, and month remained statistically significant when baseline lung function was included in the generalized estimating equation model.

The association was significant when using a 1-month interval (adjusted relative rate, 0.89; 95% CI, 0.83-0.96; P = .01), a 2-month interval (adjusted relative rate, 0.90; 95% CI, 0.83-0.96; P = .01), and a 4-month interval (adjusted relative rate, 0.91; 95% CI, 0.85-0.98; P = .02) between tests for bronchial responsiveness and physical activity.

There was no significant difference between the children with and without complete data for bronchial responsiveness regarding physical activity (P = .43), sex (P = .97), BMI (P = .50), sensitization (P = .84), household income (P = .34), and diagnosis of asthma (P = .28).

Reversibility to β_2-agonist was significantly associated with physical activity in the unadjusted analysis. However, this association did not remain when adjusted for confounders (Table II). Exhaled nitric oxide levels showed no association with physical activity (Table II). Wheezy symptoms recorded in diary cards by the parents were not associated with physical activity (Table II).

There was no interaction with use of corticosteroids at any test. No association between physical activity and diagnosis of asthma was found (P = .81, Fig 2).

The association between physical activity and bronchial responsiveness was further explored with PCA. The first 2 axes of PCA summarize the main patterns of variation (43% and 7% of the overall variability, respectively; Fig 3). The interpretation of the PCA patterns reveals a gradient of physical activity along the first PCA axis and discrimination between early and late afternoon activity along the second PCA axis. PCA shows that bronchial responsiveness was inversely correlated with the average physical activity (P = .006, Monte-Carlo permutation test; Fig 3, contours and fitted vector). PCA confirmed a significant association between physical activity and sex, as well as month of the year. No association was found between physical activity and nitric oxide level (P = .50) or reversibility to β_2-agonist (P = .37) by using PCA.

DISCUSSION

Principal findings

We showed a strong linear association between bronchial responsiveness and subclinical reduction of physical activity. A 20% increase in bronchial responsiveness implied an 11% decrease in physical activity assessed over a 4–week period. This association was independent of confounders and robust in 2 statistically different analytic approaches. This effect size of 11% from a 20% increased bronchial responsiveness could be compared with the 16% difference in physical activity measured between boys and girls, suggesting this effect size is clinically relevant.

The children had been followed prospectively from birth under close scrutiny for asthma symptoms in this longitudinal, single-center, clinical birth cohort study. Our data therefore suggest that an important but subclinical reduction in physical activity is a general phenomenon in young children with increased bronchial responsiveness and that children with such mild subclinical asthma propensity have reduced physical activity.

Using a computer to assess physical activity minute by minute over weeks provides a novel approach to gaining insight into physical activity in children and its relation to asthma.

Strengths and limitations

The primary strength of this study is the closely monitored cohort. Lung symptoms of the children were monitored in daily diary cards since birth, and the children were assessed clinically at 6–month intervals at the clinical research unit for a 2- to 3-hour study visit, including review of symptom history based on daily diary cards and objective assessment of lung function. Any symptoms of asthma were diagnosed and treated by the doctor at the clinical research unit (not the community doctors) in accordance with predefined written standard operating procedures. All mothers were familiar with asthma symptoms because they all had a history of asthma. The risk of missing asthma symptoms in this cohort is therefore less than in the ordinary clinical situation.

It adds to the validity of the conclusion that the study included a birth cohort and hence the full disease continuum from children with no lung symptoms to children with intermittent, persistent, and severe symptoms of asthma and other wheezy disorders.

It is the strength of this study that physical activity was assessed objectively by using accelerometry, a method that has been validated in several studies,[22-25] and furthermore that we assessed it continuously over a 4–week period. The bronchial responsiveness was assessed objectively by using the cold dry-air hyperventilation test and whole-body plethysmography, which we have previously developed and validated for this cohort study.[15-17]

TABLE I. Characteristics of all participants and children with and without asthma

Variable	Total	Patients with diagnosed asthma	Control subjects	*P* value
No.	253	45 (18%)	208 (82%)	–
Age (y)	5.2 ± 0.7 (3.9 to 7.3)	5.1 ± 0.7 (3.9 to 7.3)	5.2 ± 0.7 (4.1 to 6.6)	NS (P = .58)
Sex, male	126 (50%)	27 (21%)	99 (79%)	NS (P = .13)
BMI (kg · m^{-2})	15.6 ± 1.3 (12.8 to 21.4)	15.8 ± 1.4 (13.3 to 20.9)	15.6 ± 1.3 (12.8 to 21.4)	NS (P = .29)
Days recorded	26.3 ± 3.7 (7 to 28)	26.7 ± 2.0 (18 to 28)	26.2 ± 4.0 (7 to 28)	NS (P = .38)
Sensitization	77 (30%)	13 (17%)	64 (83%)	NS (P = .86)
Rhinitis	86 (34%)	25 (29%)	61 (71%)	P = .02
Medical treatment (ICS/ montelukast)	24/0	22/0	2/0	–
Activity (counts · min^{-1})	1,003 ± 277 (487 to 1,900)	1,049 ± 272 (592 to 1,900)	993 ± 278 (487 to 1,826)	NS (P = .22)
Bronchial responsiveness to cold dry-air hyperventilation (% change in sRaw)	9.3% ± 17.5 (−24.5 to 79.2; n = 81)	13.7% ± 26.5 (−15.2 to 79.2; n = 13)	8.6% ± 15.5 (−24.5 to 57.8; n = 68)	NS (P = .57)
Reversibility to β_2-agonist (% change in sRaw)	−20.0% ± 12.7 (−45.4 to 20.0; n = 118)	−24.8% ± 10.6 (−41.0 to −7.5; n = 20)	−19.0% ± 12.9 (−45.4 to 20.0; n = 98)	NS (P = .07)
Exhaled nitric oxide (ppb)	8.7 ± 6.4 (0.8 to 61.9; n = 101)	7.0 ± 4.3 (0.8 to 19.0; n = 20)	8.7 ± 6.8 (2.8 to 61.9; n = 81)	NS (P = .18)

All values are presented as means ± SDs, with ranges in parentheses, where applicable.
ICS, Inhaled corticosteroid; *NS*, not significant.

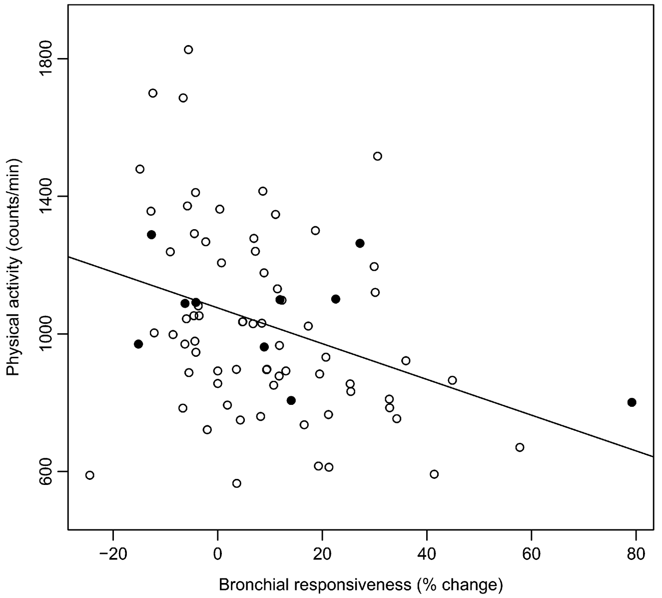

FIG 2. Association between physical activity and bronchial responsiveness. The regression line is based on data from the 81 participants with completed data for bronchial responsiveness. Asthmatic subjects are indicated by *solid circles*.

It is furthermore a strength of this study that both supervised (logistic regression) and unsupervised (PCA) methods of data analysis were applied and both confirmed that physical activity in young children decreases with increasing bronchial responsiveness.

One limitation of the study is that because of the cohort study design, bronchial responsiveness was not measured simultaneously with the 1-month assessment of physical activity but only within a 3-month period. However, sensitivity analyses of 1-, 2-, and 4-month intervals found similar results. Furthermore, a drop-out analysis found no differences between children with and without complete data.

Interpretation

Subclinical reduction in physical activity was proportional with bronchial responsiveness. The association was independent of recognized asthma. This suggests that young children can experience exercise-induced symptoms in proportion to their bronchial responsiveness that prevent them from normal physical activity levels and that this might go unnoticed, even in a carefully monitored clinical study. The effect from bronchial hyperresponsiveness is clinically relevant because its magnitude is in a comparable range as that of the sex effect on physical activity.

Increased bronchial responsiveness is a surrogate marker for increased asthma propensity. It is an intermediary asthma end point closely related to the underlying mechanisms of asthma.[26] It predicts asthma symptoms and is not influenced by variation in symptom perception or diagnostic trends.[27] Increased bronchial responsiveness might be improved by controller treatment.[10]

Exercise-induced symptoms have frequently been found to go undiagnosed. Children not receiving a diagnosis will not receive the medical treatment needed to be sufficiently physically active. Therefore the importance of screening for exercise-induced symptoms has been emphasized.[28] In particular, young children are often unable to recognize or report their exercise-induced symptoms. The activity peaks during hours when the young child is often in the care of others, who might be unobservant to such symptoms. As a consequence, exercise-induced symptoms can often go unnoticed.

It is difficult to speculate on causality, whether greater bronchial responsiveness leads to decreased physical activity or decreased physical activity leads to increased bronchial responsiveness. However, regular exercise has been found not to influence resting lung function[29] and bronchial responsiveness to methacholine.[30] This suggests that greater bronchial responsiveness leads to decreased activity. It has been argued that if asthmatic subjects are restricting their physical activity because of asthma symptoms, this indicates that the asthma is not being well controlled and steps should be taken to improve the management of the asthma.[31]

TABLE II. Results from the analyses of associations between physical activity and lung function tests, as well as asthmatic symptoms, using a generalized estimating equation model

		Unadjusted		Adjusted*	
Target variable	**No.**	***P* value**	**Relative rate (95% CI)**	***P* value**	**Relative rate (95% CI)**
Bronchial responsiveness to cold, dry-air hyperventilation	81	.007	0.89 (0.83-0.95)	.007	0.89 (0.83-0.95)
Reversibility to β_2-agonist	118	.02	0.96 (0.92-0.99)	.19	0.98 (0.94-1.01)
Exhaled nitric oxide	101	.25	0.97 (0.93-1.02)	.77	1.01 (0.96-1.06)
Asthmatic symptoms	253	.77	0.99 (0.90-1.08)	.46	0.97 (0.88-1.06)

No., Number of participants with a completed test within the chosen time limits of a maximum of 3 months between testing for physical activity and a given lung function test.
*Adjusted for sex and month.

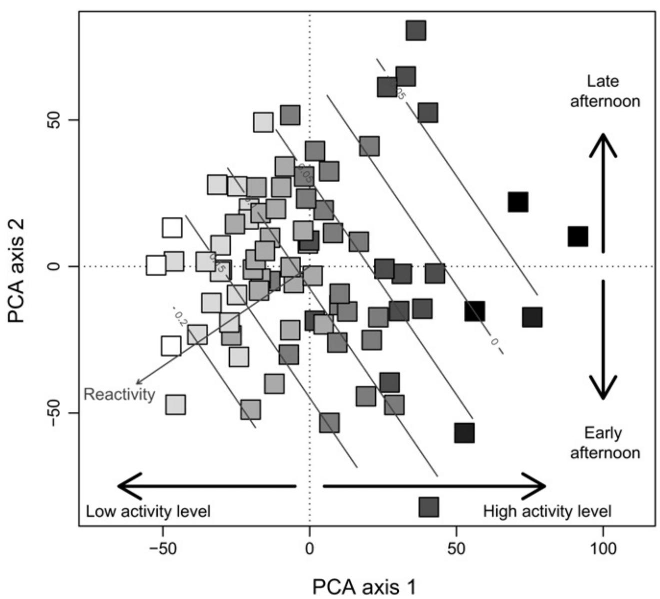

FIG 3. PCA of physical activity. Children (scores on the 2 PCA axes) are represented by *squares*. The gradient in *gray* is proportional to the average level of activity. The level of bronchial responsiveness is superimposed (vector "reactivity" and associated contours).

Recent studies have demonstrated that children and youth with asthma are less physically active than their nonasthmatic peers.[8,32-35] One of these studies used accelerometers to assess physical activity in children with newly diagnosed untreated asthma and found them to be less physically active than healthy control subjects.[34] Our approach is different because we found reduced physical activity in a cohort of subjects without symptoms classifying them as having asthma. The children qualifying for an asthma diagnosis have received a diagnosis and been treated medically according to a strict algorithm at a very early stage, which probably allowed them to be as physically active as their nonasthmatic peers in the cohort. Hence we expected not to find a difference in the level of physical activity between children with and without asthma.

It is the important finding of this study that children not classifying for a diagnosis of asthma still can have reduced physical activity in proportion to their bronchial responsiveness. Our findings might prompt an increased awareness of subclinical asthma symptoms in young children, such as exercise-induced symptoms, and a wider use of bronchial responsiveness tests. Boys were more active than girls, and this is consistent with other studies in this age group.[36-39] We found no association between physical activity and age,[37] nor did we see an association between physical activity and BMI,[40,36,39] as expected in such a narrow age range. Finally, BMI is known to exhibit less variation in young children compared with older children and adults.

The relationship between usual levels of physical activity and bronchial responsiveness has been investigated in a study of children aged 8 to 12 years that found no association between physical activity and lung function[40] and in a study of children aged 6 to 16 years that found bronchial responsiveness to be increased in asthmatic subjects with decreasing hours of exercise per week.[41] One study of adults found bronchial hyperresponsiveness to be associated with decreased physical activity.[32] Questionnaires were used to assess physical activity in these studies, and none of the studies of children focused on young children.

Accelerometry is a feasible and valid method of assessing physical activity in children.[22-24] Its feasibility was confirmed in this study by the completion of data from 253 young children 5 years of age. Even younger children can easily be studied because the method requires no cooperation. This might provide novel insights into the clinical burden in the much underserved population of young wheezy children.

The data provided by accelerometers are significantly correlated with aerobic capacity in young children[22] and energy expenditure during activity.[25] The Actical monitor used is designed for measurement of whole-body physical activity and allows detection of sedentary movements, as well as high-energy movements.[25] This method of digitized recording of physical activity minute by minute for several weeks provides a novel approach to understanding physical activity in children and its relation to asthma.

In conclusion, this study shows a strong and consistent association between physical activity and bronchial responsiveness in young children. The method used to assess physical activity might improve our understanding of physical activity in children and its relation to asthma. Our findings suggest a subclinical reduction in physical activity in young children in proportion to their bronchial hyperresponsiveness yet without clear symptoms of asthma. This should encourage an increased awareness of subclinical asthma in preschool children.

We thank the children and parents participating in the COPSAC cohort, as well as the COPSAC study team, senior statistician Christian Bressen Pipper, and technical assistant Richard Flaaten.

Clinical implications: Physical activity is essential for young children to develop adequately. Exercise-induced asthma can restrict children in their everyday life. We observed a subclinical reduction in objectively assessed physical activity in children with bronchial hyperresponsiveness.

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