

Determinants of Exercise Capacity in Children and Adolescents with Asthma: A Comparative Case-Control Study

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ABSTRACT

Background: Asthma is a chronic disease that may affect exercise capacity. Despite the variety of existing tools for assessing exercise capacity, whether patients with asthma have lower exercise capacity than healthy controls and its potential determinants are still poorly understood. **Aim:** The primary aim of this study was to identify potential determinants of exercise capacity. The secondary aim was to compare exercise capacity, pulmonary function, and muscle strength of children and adolescents with asthma with healthy controls. **Methods:** Volunteers aged 7–17 participated in the study and were divided into two groups: the asthma ($n = 60$) and the healthy control ($n = 40$). Asthma control questionnaire, six-minute walk test, pulmonary function test, maximum inspiratory (MIP) and expiratory (MEP) pressure measurements, and 30-second sit-to-stand test (30-STST) were performed. **Results:** The study showed that exercise capacity and respiratory and peripheral muscle strength were significantly lower compared to controls ($P < 0.001$, $P = 0.031$, $P = 0.001$, $P = 0.025$, respectively). Another critical finding was MIP, 30-STST, and MEP were the determinants of exercise capacity in children with asthma ($R^2 = 0.403$, $P < 0.001$). **Conclusion:** Clinicians should not ignore that exercise capacity may be reduced in children and adolescents with asthma and add assessment and training of respiratory and peripheral muscle strength in pulmonary rehabilitation programs.

KEYWORDS: Asthma, exercise capacity, peripheral muscle strength, pulmonary function, respiratory muscle strength

Key Messages

- Exercise capacity and respiratory and peripheral muscle strength were significantly lower than healthy controls in children with asthma.
- This is the first study to show that respiratory muscle strength is the determinant of exercise capacity in children with asthma.
- Even if pulmonary function test results show mostly normal patterns, respiratory and peripheral muscle strength training should be included in pulmonary rehabilitation programs.

INTRODUCTION

Asthma is a non-communicable common disease of significant global impact, carrying substantial public health implications for individuals from children to adults. Global trends demonstrate a dramatically rising prevalence of asthma among children, a phenomenon linked to heightened disease

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severity, inadequate management, and the presence of socioeconomic disadvantages.^[1] According to the Centers for Disease Control and Prevention (CDC), the prevalence of asthma is 9.6% among children aged 5–11 years, and 10.5% among those aged 12–17 years.^[2] Asthma-related common symptoms in children can be listed as wheezing, cough, shortness of breath, chest tightness, fatigue, and difficulty performing physical activities.^[3]

Exercise capacity may be defined as “the peak level of physical effort that a person can endure”. Pulmonary dysfunction, systemic inflammation, and severe dyspnea are common in respiratory diseases and can lead to progressive deterioration of physical fitness and exercise capacity.^[4] Moreover, peripheral muscle weakness, oxidative stress, nutritional imbalances, and physical inactivity also reduce exercise capacity in patients with chronic respiratory diseases.^[5] Assessing and managing exercise capacity is crucial for morbimortality and disease management in chronic respiratory diseases.^[6] Since exercise training is the only form of physical activity recommended for patients with asthma, it is reasonable to assume that their exercise capacity may be reduced. However the variety of existing tools for assessing the exercise capacity in patients with asthma, there is still no consensus on whether patients with asthma have lower exercise capacity than healthy controls.^[7,8] On the contrary, two previous studies have indicated that children with moderate-to-severe asthma exhibited reduced maximal aerobic capacity in comparison to the control group.^[9,10] Additionally, it is not yet clear what are the determinants of a possible reduction of exercise capacity. Several researchers have suggested that reduced exercise capacity may be related to a decline in pulmonary function, respiratory and peripheral muscle strength, health-related quality of life, and physical activity levels.^[11,12]

Exercise capacity in children with asthma may be assessed with clinical and laboratory tests such as cardiopulmonary exercise test, 6-minute walk test (6MWT), and shuttle walking tests. Among these tests, 6MWT is known for its simplicity, reproducibility, and cost-effectiveness. It is commonly utilized as a clinical indicator of exercise capacity and serves as a predictor of morbidity and mortality in a range of cardiopulmonary conditions.^[13] Recent studies on the clinical utility of 6MWT considered the test reliable and valid in patients with asthma.^[14] As far as we know, there are limited studies investigating the comparison of exercise capacity between children and adolescents with asthma and age-matched controls.

Considering the heterogeneous clinical presentation involved in children with asthma, A deeper understanding

of the factors that affect exercise capacity would improve the clinical management and rehabilitation programs for these patients. In the GINA 2023 guideline, while chest physiotherapy is shown as Level A evidence for symptom control and quality of life, evidence about the exercise types that may change exercise capacity, physical activity, and muscle strength is controversial.^[15] Thus, the present study aimed to provide insight into the potential determinants affecting exercise capacity in children and adolescents with asthma and compare with the healthy age-matched controls. The secondary aim was to compare exercise capacity, pulmonary function, and muscle strength of children and adolescents with asthma with healthy controls.

MATERIALS AND METHODS

Study design and participants

This was a case-control study including sixty children and adolescents with asthma and forty children without asthma, aged 7–17 years. The patients were recruited from the Pediatric Allergy and Immunology outpatient clinic. Inclusion criteria of the children and adolescents with asthma were as follows: diagnosed clinically stable asthma which requires treatment on Global Initiative for Asthma (GINA) steps 1–3,^[16] between the ages of 7 and 17 years, and able to comprehend spoken language. The patients were excluded if they had any mental, or physical disability or cardiac abnormalities that could perform the tests or had an acute exacerbation or hospitalization history in the last 4 weeks. The inclusion criteria for healthy children were being between the ages of 7 and 17 years and having the ability to understand spoken language. Children with diagnosed comorbidities that prevented them from performing the tests were excluded. Figure 1 presents the flow diagram of the study.

Data were collected between January and June 2023. The Human Research Ethics Committee of Biruni University (protocol number: 2023/82-01) approved the study and conducted by the Declaration of Helsinki. It was registered on the ClinicalTrials.gov website under registration number NCT05963919. The parents or legal guardians provided written informed consent.

Outcome measures

Participants' demographic characteristics were recorded using a standard form, which collected information on gender, age, height, weight, age at diagnosis, presence of chronic illness, medications, and the number of asthma attacks.

Participants performed an asthma control questionnaire, 6MWT, pulmonary function test (PFT), maximum

inspiratory (MIP) and expiratory (MEP) pressure measurements, and 30-second sit-to-stand test (30-STST).

The Asthma Control Test (ACT) is a survey designed to evaluate asthma control from a patient's perspective. The ACT evaluates limitations in activity and symptoms experienced over the preceding 4 weeks. Response choices span from 1 (indicating the poorest) to 5 (indicating the best). The maximum attainable score for the ACT is 25. Asthma is considered to be well-controlled when the score exceeds 20, partially controlled when it falls within the range of 16–19, and uncontrolled when the score is equal to or less than 15.^[17]

The 6MWT has been used by the American Thoracic Society (ATS) as a criterion for determining exercise capacity.^[13] The participants were instructed to walk as quickly as possible at their own pace without running for 6 minutes along a 30-meter straight corridor. Before and following the test, a series of physiological measurements were taken, including oxygen saturation (SpO₂), heart rate, respiratory rate, blood pressure dyspnea, fatigue (assessed using the Modified Borg Scale), and leg pain (assessed using the Visual Analogue Scale). The distance walked in 6 minutes was recorded.

Pulmonary function tests were conducted using a spirometer (COSMED Pony FX), following the ATS and European Respiratory Society (ERS) guidelines.^[18] The measured parameters, including forced vital capacity (FVC), forced expiratory volume in one second (FEV1), FEV1/FVC ratio, and peak expiratory flow (PEF), were reported as percentages of the predicted values.

MIP and MEP were determined using an electronic, mobile device (MicroRPM, Micro Medical; UK). The maximum value from three attempts, with variations of less than 5%, was accepted as the MIP and MEP values for the participants. The measurements were repeated for both and the best value was recorded as cm H₂O.^[19]

The 30-STST was performed to assess the peripheral muscle performance of the lower limbs. A standard armless chair, 46 cm in height, was used for the test. Participants were instructed to sit on the chair and cross their arms over their chest. They were guided to rise fully until their legs were extended and then to return to a seated position until their buttocks made distinct contact with the chair, aiming to complete as many cycles as possible within 30 seconds. The number of completed sit-to-stand repetitions within 30 seconds was recorded.^[20]

Statistics and sample size

Data were analyzed using the IBM SPSS v.26 statistical software (SPSS Inc., USA). The normality of the data distribution was evaluated using the Kolmogorov-Smirnov test. A Chi-square test was used to compare categorical variables between groups. For intergroup comparisons, either the Independent *T*-test or the Mann–Whitney *U* test was applied, depending on the data distribution. Effect size was determined using Cohen's *d*, and 95% confidence intervals (95% CI) were calculated and reported as the mean difference (MD) with a 95% CI for each variable to support statistical inference. Statistical significance was set at $P < 0.05$ for all analyses. Pearson or Spearman correlation analysis was performed based on the normality of continuous data to examine the relationship between exercise capacity and PFT, as well as respiratory and peripheral muscle strength. Correlations were classified by coefficient (*r*) as weak ($r < 0.3$), moderate ($r = 0.3–0.5$), or strong ($r = 0.5–1.0$). To assess which predictors contributed to the prediction of exercise capacity, a multivariable linear regression model was used. Variables presenting the highest correlation coefficient (*r*) with the exercise capacity were included in the model. The forward stepwise method was used for variable selection. Only the model with the highest R^2 (coefficient of determination) is shown.

Table 1: The demographic and clinical characteristics of all participants

	Asthma Group (<i>n</i> =60)	Control Group (<i>n</i> =40)	<i>P</i>
Age (year)	12.31±2.78	10.95±3.42	0.072
Gender			
Female	36 (60%)	25 (62.5%)	0.462
Male	24 (40%)	15 (37.5%)	
Body composition			
Height (cm)	146.44±34.50	144.35±30.12	0.088
Weight (kg)	47.57±18.21	46.85±19.51	0.074
BMI (kg/m ²)	20.50±4.12	19.03±4.74	0.056
Age at diagnosis (year)	4.45±3.35		
Number of asthma attacks in previous year	0.8±1.2	-	-
ACT		-	-
Controlled	15 (25%)		
Partially controlled	27 (45%)		
Uncontrolled	18 (30%)		
Drugs, number of users, <i>n</i> (%)			
Inhaled corticosteroids	33 (55%)		
β ₂ agonists	45 (75%)		

ACT: Asthma control test; BMI: Body mass index; cm: centimeter; kg: kilogram; Data are presented as mean±standard deviation or *n* (%). * $P \leq 0.05$

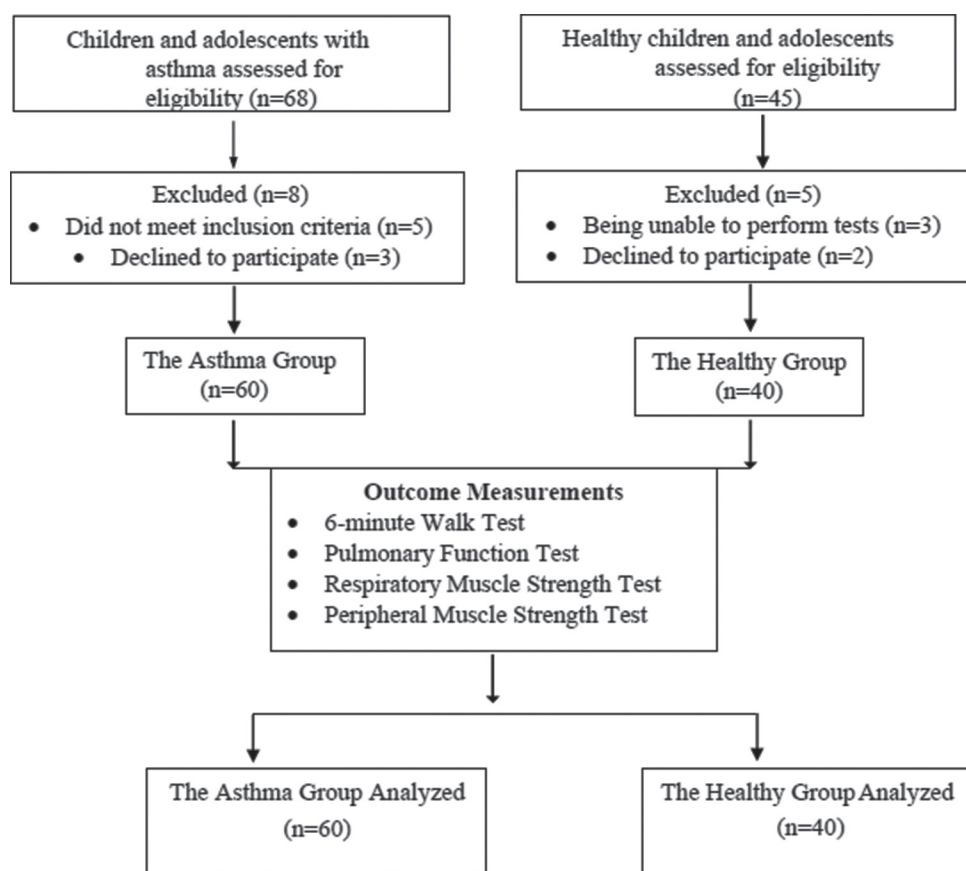


Figure 1: CONSORT flow diagram

Table 2: Comparison of functional capacity, pulmonary function, respiratory and peripheral muscle strength between asthma and control group

	Asthma Group (n=60)	Control Group (n=40)	P	95% CI		Effect size (Cohen's d)
				Lower	Upper	
Functional capacity						
6MWT distance (m)	544.25±54.37	596.47±52.36	<0.001	-78.94	-25.50	0.978
Pulmonary function						
FVC (% pred)	97.68±15.33	99.45±12.45	0.321	-4.04	1.45	0.126
FEV ₁ (% pred)	98.68±16.17	98.5±11.7	0.748	-2.45	0.89	0.012
FEV ₁ /FVC (%)	115.98±7.07	113.2±5.9	0.235	-3.14	4.10	0.426
PEF (% pred)	87.12±15.73	90.45±6.8	0.199	-7.36	1.36	0.299
Respiratory muscle strength						
MIP (cmH ₂ O)	68.71±23.25	81.95±18.81	0.031	-35.40	-13.38	0.626
MEP (cmH ₂ O)	69.48±23.44	87±14.67	0.001	-29.74	-8.13	0.896
Peripheral muscle strength						
30-STST	19.65±4.64	25.55±3.56	0.025	-10.45	-3.80	1.426

FEV₁: forced expiratory volume in 1s; FVC: forced vital capacity; m: meter; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; PEF: peak expiratory flow; pred: predicted; 6MWT: 6-minute walk test; 30-STST: 30-second sit-to-stand test. Data are presented as mean±standard deviation (%95 confidence interval). *P≤0.05

G*Power 3.1 software was used for calculating the sample size. (University of Düsseldorf, Germany). Reimberg *et al.*^[4] reported that there was a significant difference in exercise capacity between children and adolescents with asthma and healthy peers in which the effect size was 0.692 (790 ± 222 m vs 950 ± 240 m). We

calculated that at least 34 participants per group would be required to detect this difference with %80 power and 95% confidence in the study.

RESULTS

Sixty participants with asthma and 40 healthy

controls, matched for age and gender, completed the assessments [Figure 1]. The demographic and clinical characteristics of all participants are shown in Table 1. The asthmatic children and healthy controls were similar in terms of gender, age, weight, height, and body mass index.

Children and adolescents with asthma had lower exercise capacity (544.25 ± 54.37 and 596.47 ± 52.36 ; $P < 0.001$), MIP (68.71 ± 23.25 and 81.95 ± 18.81 ; $P = 0.031$), MEP (69.48 ± 23.44 and 87 ± 14.67 ; $P = 0.001$), and 30s-STST (19.65 ± 4.64 and 25.55 ± 3.56 ; $P = 0.025$) compared with the control group, respectively. There was no statistically significant difference between the two groups in terms of PFT parameters [Table 2].

There was a moderate correlation between the 6MWT distance and MEP ($r = 0.368$, $P = 0.002$) and 30-STST ($r = 0.380$, $P = 0.001$). Also, a strong correlation was observed between 6MWT distance and MIP ($r = 0.522$, $P < 0.001$). No statistically significant correlation was found between the 6MWT distance and any spirometric parameters [Table 3].

A multiple linear regression model was utilized to determine the factors that were independently

associated with the 6MWT distance. MIP, the number of 30-STST, and MEP were identified as the independent predictors of 6MWT distance, explaining 40% of the variance ($R = 0.635$, $P < 0.001$) [Table 4].

DISCUSSION

The present study showed that exercise capacity and respiratory and peripheral muscle strength were significantly lower in children and adolescents with asthma compared to healthy controls. Another critical finding was MIP, 30-STST, and MEP were the determinants of 6MWT distance. A model that consists of these three variables explained 40% of the variance in exercise capacity in patients with asthma.

A reduced exercise capacity which was assessed by 6MWT was found in children and adolescents with asthma compared to the healthy controls in the present study. This seems to agree with previous studies showing that 6MWT distance was significantly lower in children and adolescents with asthma than in healthy children,^[4,21] Teoh *et al.*^[22] found that up to 30% of children and adolescents with asthma experienced exercise limitations compared to predicted values for healthy individuals of the same age group. They concluded that these limitations were influenced by multiple factors in this population. This issue remains controversial because according to few studies, no evidence of impaired exercise capacity was detected.^[7,23] A possible explanation for various results could be related to several factors including different drug treatment modalities, degree of disease severity, disease control, previous exercise capacity levels, and use of various measurement methods. The high proportion of our patients classified as partially controlled and uncontrolled asthma according to both ACT and C-ACT scores appears to support this hypothesis.

Previous studies showed that several factors may influence the exercise capacity of asthmatic children; among them, peripheral muscle strength is rarely cited.^[10,24] The findings of this study demonstrate a reduction in peripheral muscle strength among children and adolescents with asthma in comparison to their healthy counterparts. Recent studies have investigated a decline in peripheral muscle strength in various chronic

Table 3: Correlation of the functional capacity with the pulmonary function, respiratory, and peripheral muscle strength

	6MWT (n=60)	
	<i>r</i>	<i>P</i>
Pulmonary function		
FVC (% pred)	0.101	0.406
FEV ₁ (% pred)	-0.053	0.664
FEV ₁ /FVC (%)	-0.073	0.546
PEF (% pred)	-0.014	0.911
Respiratory muscle strength		
MIP (cmH ₂ O)	0.522	<0.001
MEP (cmH ₂ O)	0.368	0.002
Peripheral muscle strength		
30-STST	0.380	0.001

FEV₁: forced expiratory volume in 1s; FVC: forced vital capacity; m: meter; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; PEF: peak expiratory flow; pred: predicted; 6MWT: 6 minute walk test; 30-STST: 30-second sit-to-stand test.

* $P \leq 0.05$

Table 4: Multiple linear regression model for predicting the functional capacity

	B	Standard Error of B (95% CI)	Standardized Beta Coefficient	<i>P</i>	<i>R</i> ²
Constant	391.454	341.50-441.39		<0.001	0.403
MIP (cmH ₂ O)	1.061	0.439-1.683	0.454		
MEP (cmH ₂ O)	0.029	-0.596-0.653	0.012		
30-STST	3.964	1.648-6.280	0.339		

MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; 30-STST: 30-second sit-to-stand test. * $P \leq 0.05$

respiratory diseases, including cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD).^[25,26] These researchers stated that the possible mechanisms of impairing peripheral muscle strength might be the use of long-term corticosteroids, physical inactivity, malnutrition, and hypoxemia. While peripheral muscle strength plays a crucial role in physical fitness, there has been limited research conducted on its impact on children with asthma. Several studies showed a decrease in quadriceps muscle strength in children and adolescents with asthma compared to healthy controls.^[10,27] In contrast to previous findings, Reimberg *et al.*^[4] showed that muscle strength assessed by a quadriceps muscle-specific measurement method did not differ between asthmatic and healthy children. The fact that we assessed peripheral muscle strength with the 30-STS, which is also used to determine exercise capacity, may have played a role in the low peripheral muscle strength of asthmatic children with already low exercise capacity. Another important finding regarding peripheral muscle strength was that 30-STS was a robust independent predictor of exercise capacity. Similarly, several authors have reported to relationship between exercise capacity and upper or lower muscle strength in patients with COPD.^[28] Similarly, a recent study by Rovedder that muscle strength was found significantly correlated with exercise capacity in adults with CF.^[29] A recent study has been carried out on a relationship between lower limb muscle strength with 30-STST in children and adolescents.^[30] No single study exists that uses 30-STST in children and adolescents with asthma for determining lower limb muscle strength and showing a relationship with exercise capacity. To the best of our knowledge, it has been demonstrated for the first time that lower extremity strength was assessed with 30-STST, and its relationship with exercise capacity in children and adolescents with asthma was shown.

According to the hyperinflation, some biomechanical changes were expected in children and adolescents with asthma in the literature. For instance, as a result of an increment in lung hyperinflation and functional residual capacity, the respiratory mechanics are varied, and the diaphragm is getting flat. This diaphragm flattening creates a mechanical disadvantage consequently, the respiratory muscle strength may decrease.^[31] Despite all these theoretical models, it is not yet clear in the literature about the decrease of alteration respiratory muscle strength in children with asthma. In terms of respiratory muscle strength, two previous studies found no significant differences between healthy children and those with mild asthma.^[32] In contrast to earlier findings, few studies have explored that respiratory muscle strength is weakened in children and adolescents

with asthma.^[31,33] Thus, decreased MIP and MEP values in our asthma group compared to the healthy controls may be the result of possible hyperinflation even if we could not assess hyperinflation in our study. The present findings are consistent with the results of Dassios *et al.*^[33] showing that the respiratory muscle strengths of children with CF with normal PFT values were lower than healthy children. Another possible explanation for that is the use of corticosteroids leads to steroid-induced myopathy. Numerous studies have pointed out a relation between the use of even low doses of corticosteroids and decreased respiratory muscle strength.^[34,35] One of these studies has indicated that oral corticosteroid-dependent asthma patients exhibited lower MIP compared to the non-dependents, although both groups almost have similar results of PFT.^[34] In the present study, the presence of a high number of children who use corticosteroids may also support this assumption.

This study also demonstrated a positive correlation between respiratory muscle strength and exercise capacity. Until recently, there has been no reliable evidence of the relationship between respiratory muscle strength and exercise capacity in children with asthma, but there are some studies evaluating other chronic diseases.^[36,37] The current findings align with other studies that associate respiratory muscle strength with exercise capacity. The primary underlying mechanism responsible for this relation is systemic inflammation leading to histological changes. This change causes an impairment in the proportion of the type of muscle fibers resulting in a decrease in strength production and fatigue endurance further impairing muscle function.^[38] Another possible mechanism is that in subjects with respiratory muscle weakness, increased respiratory effort, especially during exercise, may increase oxidative metabolic stress in respiratory muscles and local metaboreflex stimulation. As a result, increased blood flow to the respiratory muscles may occur, while perfusion to the peripheral muscles is reduced, leading to early fatigue.^[39] The fact that the patients included in the study had a chronic respiratory disease for a relatively long time may have caused the mentioned physiological changes.

We could not show a difference in terms of PFT with the healthy controls and the relationship between PFT and exercise capacity. Several authors have reported that only PFT results poorly reflect patients' daily experiences, and are insufficient to assess the impact of asthma on the individual concern.^[21,40] Contrary, there are only a few studies that found a relationship between PFT and exercise capacity in children with asthma. One of these studies investigated asthma children who have FEV₁ below 80%, despite the value of FEV₁ was not

detected as an excluded criterion.^[9] The authors attributed their results to longer exposure to the disease and the presence of obstruction. Furthermore, the mean FEV₁ value in our study was 98%. The other study interested in asthmatic children with obesity revealed an association between PFT and exercise capacity. This contradictory result may be due to the mean body mass index of the children and adolescents with asthma included in the study being in the normal weight category.^[40] This contradictory result may be due to the mean body mass index of the children and adolescents with asthma included in the study being in the normal weight category.

Several limitations need to be considered in the study. Although we assessed peripheral muscle strength with the 30-STST, a clinic-based test, the fact that we could not use a laboratory-based test can be considered a limitation. Another limitation is the lack of assessment of additional factors that could influence the results of exercise capacity such as the level of physical activity or lung hyperinflation.

CONCLUSION

In conclusion, the findings of this study revealed that children and adolescents with asthma have reduced exercise capacity, as well as decreased respiratory and peripheral muscle strength, compared to healthy controls. The second major finding was that exercise capacity appears to be determined by respiratory and peripheral muscle strength. Thus, we suggest not ignoring that exercise capacity may be reduced in children and adolescents with asthma and adding assessment and training of respiratory and peripheral muscle strength in pulmonary rehabilitation programs even if PFT results showed mostly normal patterns.

Author contributions

Meltem KAYA: Conception, design, data collection, analysis, literature review, writing of the manuscript

Hikmet UCGUN: Conception, design, data collection, analysis, literature review, writing of the manuscript

Betul GEMICI KARAASLAN: Design, referral of the patients

Ayca KIYKIM: Design, supervision, referral of the patients, critical review of the manuscript

Hilal DENIZOGLU KULLI: Conception, design, supervision, data collection, analysis, critical review of the manuscript

The manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work.

Approval of ethics committee

The study was approved by Biruni University's ethics committee (protocol number: 2023/82-01) and registered on the ClinicalTrials.gov website (registration number: NCT05963919). It was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants whose data were used in the study.

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Conflicts of interest

There are no conflicts of interest.

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