Andrey Wirgues de Sousa

**Fenótipos clínicos e fatores de risco para obstrução fixa das
vias aéreas em crianças e adolescentes com asma**

Tese apresentada à Faculdade de Medicina
da Universidade de São Paulo para obtenção
do título de Doutor em Ciências

Programa de Fisiopatologia Experimental

Orientador: Prof. Dr. Celso Ricardo
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Dados Internacionais de Catalogação na Publicação (CIP)

Preparada pela Biblioteca da
Faculdade de Medicina da Universidade de São Paulo

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Sousa, Andrey Wirgues de
Fenótipos clínicos e fatores de risco para
obstrução fixa das vias aéreas em crianças e
adolescentes com asma / Andrey Wirgues de Sousa. --
São Paulo, 2020.
Tese (doutorado) -- Faculdade de Medicina da
Universidade de São Paulo.
Programa de Fisiopatologia Experimental.
Orientador: Celso Ricardo Fernandes de Carvalho.

Descritores: 1.Pneumopatias 2.Condicionamento
físico humano 3.Exercício físico 4.Sedentarismo
5.Acelerômetro

USP/FM/DBD-298/20

Responsável: Erinalva da Conceição Batista, CRB-8 6755

Dedicatória

Dedico a DEUS, por colocar-me no seio de uma família gloriosa e sempre me dar saúde para que eu possa atingir meus objetivos de vida.

A minha esposa Luciana Wirgues, que me faz sentir-se o homem mais amado do universo com seus carinhos e demonstrações de amor, a essa linda mulher que me deu a bênção de ter uma filha, a essa companheira que está ao meu lado todos os dias e que nunca me deixa sentir-se sozinho, a você Luciana, que saiu do bom e tranquilo interior do estado para vir morar na tumultuada capital paulista, me trazendo força e apoio para que eu fosse atrás dos meus objetivos, enfim, a você amor, pessoa a qual sempre agradeço a DEUS por ter colocado em minha vida. Simplesmente amo você.

A minha amada filha Ana Clara Wirgues que de forma natural, me mostra todos os dias o poder do amor. A essa menina que tem o sorriso mais encantador do mundo e que enche meu coração de alegria. A ela que todos os dias me faz sentir o melhor pai do mundo quando diz “papai, eu te amo”. Papai também te ama, filha.

A meus pais Zildo Maria de Sousa e Elizabeth de Fátima Wirgues de Sousa, por me conceber a vida e a criação em todos esses anos de vida. Pais, que juntos engravidaram para que um dia eu pudesse vir ao mundo. Pais, que juntos sentiram a emoção do meu primeiro choro ao nascer e que certamente choraram junto comigo. Pais, que juntos acordaram várias noites para me alimentar. Pais, que juntos suaram a camisa para que eu pudesse ter uma bela infância e adolescência. Pais, que juntos me educaram para que tornasse um homem de

princípios. Pais, que até hoje trazem a alegria e felicidade de viver em família com muito amor. Pais, AMO muito vocês.

A minha avó Ivete Wirgues que sempre será minha segunda mãe, uma mulher batalhadora que até hoje tem uma vida ativa, graças à saúde e fé em DEUS. Saúde que não foi abalada mesmo com as várias travessuras dos netos quando todos se juntavam em sua casa, é uma “vovó” de fibra. Muitíssimo obrigado.

Ao meu avô André Wirgues (in memoriam) que ajudou na minha educação quando criança, a primeira pessoa que me ensinou a dirigir, a pessoa que me ensinava a jogar futebol e montar em cavalos. Obrigado por todas essas diversões gostosas de quando criança. Saudade do Senhor “vovô”.

A minha avó Olga Sousa (in memoriam), que nos ensinou o caminho da fé divina e sempre orava por todos da família, e de onde estiver com certeza continua orando pela nossa benção.

Ao meu avô Benedito Sousa (in memoriam), que infelizmente não tive o prazer de conhecê-lo, mas que ensinou a meu pai ser homem digno, honesto e de boa índole, independentemente de ser magro ou gordo, bonito ou feio, alto ou baixo. Ensinaamentos que como DNA, recebi com muita maestria de meu pai.

Aos meus padrinhos Francisco Moreni (in memoriam) e Rosi Moreni, que sempre me apoiaram na vida, sempre me deram força para que eu fosse atrás de meus objetivos. Nunca esquecerei o que vocês fizeram por mim. Obrigado.

Amo todos vocês!!!

Agradecimentos

Ao meu orientador Prof. Dr. Celso Ricardo Fernandes de Carvalho que primeiramente me ofereceu uma oportunidade de fazer primeiramente o mestrado e posteriormente o doutorado. Professor, que teve paciência em me receber várias vezes em sua sala, corrigir meus erros e lapidar os artigos, para hoje eu pudesse estar realizando esse sonho.

A Dra. Anna Lúcia Cabral que me acolheu maravilhosamente bem em outubro de 2008 até 2020, repartiu todo seu conhecimento teórico, forneceu espaço e pacientes para que o projeto saísse do papel. Serei eternamente grato a ti “Dra Anna” pela confiança depositada no meu trabalho, com livre acesso ao seu consultório.

Ao Prof. Dr. Milton Arruda Martins por acreditar em nosso trabalho e fornecer material suficiente para a pesquisa.

A todos os colegas do grupo LIFFE (Laboratório de Investigação em Fisioterapia e Fisiologia do Exercício), pela ajuda nas reuniões clínicas e dicas de melhoria na construção do projeto de pesquisa. Agradeço especialmente ao Ronaldo Aparecido Silva pelo apoio na condução de maneira cega do teste de esforço cardiopulmonar dos pacientes.

Aos queridos pacientes, que acreditaram e confiaram na pesquisa contribuindo para minha formação acadêmica.

Finalmente, agradeço a toda equipe do ECG-HC pelo apoio na realização dos testes de esforço cardiopulmonar. Sou muito grato à Marlene Silveira pela solicitude e dedicação para que os testes de esforço cardiopulmonar fossem agendados. Meu muito obrigado em especial vai aos doutores Alfredo José da Fonseca e José Grindler que cederam espaço, equipamento e o tempo de trabalho deles para cuidarem da parte cardiológica dos pacientes durante o teste de esforço cardiopulmonar.

Epígrafe

*“A conquista da credibilidade é um exercício diário baseado na coerência
entre palavras e atos”.*

Cika Parolin

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Abreviaturas dos títulos dos periódicos de acordo com *List of Journals Indexed in Index Medicus*.

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Apêndice

Outras atividades relevantes

Lista de abreviações

AF	Atividade física
AFMV	Atividade física moderada a vigorosa
BD	Broncodilatador
bpm	Batimentos por minutos
C-ACT	<i>Childhood-Asthma Control Test</i>
CI	Corticosteroide inalatório
CO	Corticosteroide oral
cm	Centímetro
cmH ₂ O	Centímetro de água
CO ₂	Dióxido de carbono
CVF	Capacidade vital forçada
d	Dia
FAO	<i>Fixed Airflow Obstruction</i>
FCmáx	Frequência cardíaca máxima
HCFMUSP	Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo
HIDV	Hospital Infantil Darcy Vargas
IMC	Índice de massa corporal
kg	Quilograma
kgf	Quilograma força
KU	Mil unidades
L	Litros
LABA	Beta-agonista de longa duração
LIN	Limite inferior da normalidade

m ²	Metros ao quadrado
min	Minutos
MMII	Membros inferiores
mL	Mililitros
MMSS	Membros superiores
n	Número amostral
NAF	Nível de atividade física
O ₂	Oxigênio
PAQLQ	Pediatric Asthma Quality of Life Questionnaire
PE _{máx}	Pressão expiratória máxima
PETCO ₂	Pressões de CO ₂ ao final da expiração
PETO ₂	Pressões de O ₂ ao final da expiração
PI _{máx}	Pressão inspiratória máxima
PuO ₂	Pulso de oxigênio
QR	Coeficiente respiratório
RB	Remodelamento brônquico
rpm	Rotação por minuto
TECP	Teste de esforço cardiopulmonar
UI	Unidades internacionais
VC	Volume corrente
VEF ₁	Volume expiratório forçado no primeiro segundo
VO ₂	Consumo de oxigênio
W	<i>Watts</i>
y	<i>Years</i>

Lista de símbolos

% Porcentagem

µg Micrograma

Lista de Siglas

GINA	<i>Global Initiative for Asthma</i>
SUS	Sistema Único de Saúde

Resumo

Sousa AW. Fenótipos clínicos e fatores de risco para obstrução fixa das vias aéreas em crianças e adolescentes com asma [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2020.

Introdução: A asma é uma doença inflamatória crônica das vias aéreas com diferentes fenótipos. Um dos fenótipos da asma é a obstrução das vias aéreas, que pode ser reversível espontânea ou com o tratamento. Entretanto, alguns indivíduos com asma desenvolvem obstrução fixa das vias aéreas (FAO), mesmo com o tratamento adequado. **Objetivo:** Este projeto de pesquisas foi realizado em 2 fases. A primeira fase teve 2 estudos e os objetivos foram: identificar os fenótipos e os fatores de risco para o desenvolvimento da FAO em crianças e adolescentes com asma, respectivamente. A segunda fase foi composta por 1 estudo e o objetivo foi: comparar o nível de atividade física (NAF), a potência aeróbia, a força muscular e a qualidade de vida de adolescentes portadores de asma com FAO e não-FAO. **Método:** Nas duas fases do estudo, os indivíduos deveriam ter o diagnóstico de asma de acordo com os critérios do GINA, estar em tratamento medicamentoso de asma no ambulatório do Hospital Infantil Darcy Vargas, há pelo menos, 12 meses e idade entre 6 a 18 anos. Na primeira fase, o estudo dos fenótipos da asma foi observacional retrospectivo e a análise de *cluster* foi feita por meio das variáveis da doença. O estudo dos fatores de risco para a FAO foi observacional prospectivo com 4 anos de seguimento. A FAO foi caracterizada por VEF₁/CVF menor que o limite inferior da normalidade, mesmo após tratamento com corticoide inalatório e oral, por 7 dias. As variáveis analisadas para detectar os

fatores de risco para o desenvolvimento da FAO foram: dados antropométricos, história pregressa da asma, hospitalizações, exacerbações, a prova de função pulmonar e imunoglobulina E (IgE) total e específica. A segunda fase do estudo é subsequente a primeira fase e trata-se de um estudo observacional transversal. Nesta fase foram incluídos adolescentes com asma de 12 a 18 anos, divididos em dois grupos: FAO e não-FAO. Foram avaliados os fatores de saúde relacionados ao NAF, a potência aeróbica, a força muscular respiratória e periférica e a qualidade de vida. **Resultado:** Na primeira fase, o estudo dos fenótipos incluiu 306 crianças e adolescentes com asma, sendo dividida em 3 *clusters*: função pulmonar normal, alta inflamação com função pulmonar normal e função pulmonar alterada. No estudo dos fatores de risco para FAO foram incluídos 428 pacientes e mostrou que a incidência da FAO na infância é de 9,5% e varia conforme a gravidade da asma. Os principais fatores de risco para o desenvolvimento da FAO foram a gravidade da asma e a exacerbação frequente. Na segunda fase, foram incluídos 41 pacientes (20 do grupo FAO e 21 do grupo não-FAO). Os resultados mostraram que o NAF, a potência aeróbia, a força muscular periférica e a qualidade de vida foram similares entre os adolescentes com FAO e não-FAO. Por outro lado, o grupo FAO apresentou maior força muscular expiratória do que o grupo não-FAO. **Conclusão:** Crianças e adolescentes com asma apresentam função pulmonar e inflamação como os principais fenótipos clínicos da doença. A gravidade da asma e exacerbação frequente foram os principais fatores de risco para o desenvolvimento da FAO. No entanto, o desenvolvimento da FAO pode não reduzir o NAF, a potência aeróbia, a força muscular periférica e a qualidade de vida frente aos seus pares não-FAO.

Descritores: Pneumopatias; Função Pulmonar; Condicionamento físico; Sedentarismo; Acelerômetro.

Abstract

Sousa AW. Clinical phenotypes and risk factors for fixed airflow obstruction in children and adolescents with asthma [thesis]. São Paulo: “Faculdade de Medicina, Universidade de São Paulo”; 2020.

Background: Asthma is a chronic disease characterized by airway inflammation, and phenotypes distinct. Airflow obstruction is one of clinical phenotype of the asthma, and it can be reversed either spontaneously or with pharmacological treatment. However, some subjects with asthma can develop fixed airflow obstruction (FAO), regardless of treatment. **Aim:** This research was performed in 2 phases. The first phase included 2 papers, and the aim were: to identify asthma phenotypes and risk factors for FAO development, respectively. The second phase had 1 paper and the aim was: to compare physical activity level (PAL), aerobic fitness, muscle strength and quality of life in the adolescents with FAO and their non-FAO peers. **Method:** In both phases, the subjects should have asthma diagnose according GINA, be in asthma treatment in the children Darcy Vargas hospital, at least, 12 months, and age to 6 from 18 years old. At the first phase, the asthma phenotypes' study was a retrospective observational study, and the cluster analysis were performed according asthma variables. The risk factor for FAO was a prospective observational cohort study with a 4-year follow-up. The FAO was defined by a ratio of the forced expiratory volume in the first second to the forced vital capacity (FEV_1/FVC) below the lower limit of normal (LLN), even after inhaled and oral corticosteroid treatment, per 7 days. The variables analyzed to detect the risk factors for FAO development were: anthropometric data, asthma history, hospitalization, exacerbation, lung function

test, and total and specific immunoglobulin E. The second phase had 1 paper, and this was a cross-sectional study. In this phase was included adolescents with asthma, age to 12 from 18 years old, and two groups apart (FAO and non-FAO). The PAL, aerobic fitness, muscle strength and quality of life was evaluated in both groups. **Results:** At the first phase, the phenotype's study included 306 children and adolescents in the 3 clusters. The clusters were: normal lung function, high inflammation with normal lung function and modified lung function. The risk factors for FAO's study screened 428 subjects and showed 9.5% of FAO incidence in children and adolescents with asthma. The main risk factors for FAO development were: asthma severity and frequent exacerbation. At the second phase, 41 subjects were included (21 in the FAO and 20 in the non-FAO group). Both groups presented similar PAL, aerobic fitness, muscle strength and quality of life. On the other hand, the FAO group showed more expiratory muscle strength than non-FAO group. **Conclusion:** Children and adolescents presented lung function and inflammation as asthma phenotype. Asthma severity and frequent exacerbation are the main risk factors for FAO development. However, the FAO development cannot decrease PAL, aerobic fitness, peripheral muscle strength and quality of life.

Descriptors: Pneumopathies; Lung Function; Aerobic fitness; Sedentary; Accelerometer.

1. Introdução

1.1 Asma: definição

A asma é uma doença inflamatória cônica das vias aéreas e heterogênea na qual participam muitos elementos celulares que são responsáveis pela hiperresponsividade das vias aéreas [GINA 2020]. O paciente apresenta episódios recorrentes de sibilância, dispneia, aperto no peito e tosse, principalmente à noite ou pela manhã [GINA 2020]. A limitação ao fluxo aéreo é difusa, variável e, na maioria das vezes, reversível espontaneamente ou com tratamento farmacológico [GINA 2020]. As manifestações clínicas podem ser controladas com o tratamento apropriado, ocorrendo apenas crises ocasionais e raras exacerbações. A classificação da gravidade da asma nos pacientes em tratamento é dada pelos sintomas noturnos e diurnos, medicação, frequência de exacerbações, valores do volume expiratório forçado no primeiro segundo (VEF_1) e grau de limitação à prática de atividade física [GINA 2020].

1.2 Epidemiologia

A asma atinge cerca de 334 milhões de indivíduos em todo mundo e sua prevalência varia de 5 a 32% [GINA 2020]. No Brasil, a prevalência dos sintomas de asma é cerca de 23% em crianças e adolescentes [BARRETO et al. 2014]. Esta prevalência de asma pode variar de 12 a 29% nas diferentes capitais brasileiras [SOLÉ et al. 2014]. Nos últimos anos, a prevalência da asma está aumentando [BARRETO et al. 2014; NUNES et al. 2017], entretanto, as internações pela doença diminuíram cerca de 50% no Sistema Único de Saúde (SUS) [DUARTE et al. 2015]. A diminuição do número de internações gera

economia aos cofres públicos e a atenção básica a saúde pode evitar cerca de 30% das internações hospitalares [DUARTE et al. 2015; CARDOSO et al. 2017]. Evidências mostram que a queda do número de internações pode ocorrer pelo melhor manejo do tratamento da asma, tais como: o acesso a ambulatórios de referência, o fornecimento de medicamentos e a programas de educação [DUARTE et al. 2015; SOUZA-MACHADO et al. 2010; BRANDÃO et al. 2009].

1.3 Gravidade da asma

A gravidade da asma é avaliada retrospectivamente a partir do tratamento requerido para controlar os sintomas e exacerbações da doença [GINA 2020]. A avaliação da gravidade da asma é feita por meio da frequência e intensidade dos sintomas, função pulmonar e tolerância ao exercício [GINA 2020]. O objetivo principal é a determinação do tratamento mínimo efetivo para o controle da doença [GINA 2020]. A gravidade da asma é tida conforme tipo e dose de medicamento e dividida em classificações: Asma leve (*steps* 1 e 2), o paciente requer tratamento com baixa dose de corticoide inalatório. Asma moderada (*step* 3), o paciente requer tratamento com moderada dose de corticoide inalatório associado ao beta-agonista de longa duração (em inglês LABA). Asma grave (*steps* 4 e 5), o paciente requer tratamento com altas doses de corticoide inalatório associado ao LABA [GINA 2020].

1.4 Fenótipos

Em 1911, o termo fenótipo foi descrito pela primeira vez como sendo uma resultante da interação entre os genes e o ambiente, onde o ambiente poderia modificar as características dos genes [JOHANNSEN 1911]. Já em 1999, o

conceito de fenótipo foi atualizado e até hoje segue sendo definido como características observáveis de um indivíduo que resulta da interação dos fatores relacionados a uma população [DAWKINS 1999]. Essas características podem ser morfológicas, químicas, biológicas e comportamentais [DAWKINS 1999].

A busca pelo entendimento dos fenótipos é importante para melhorar o entendimento dos mecanismos das doenças e poder personalizar o tratamento para cada indivíduo [WOJCZYNSKI & TIWARI 2008]. Sendo assim, os fenótipos vêm sendo descritos por alguns estudos [CORHAY et al. 2014; VESTBO et al. 2014]. Na asma, os fenótipos são descritos pelos dos sintomas clínicos, exacerbações, resposta ao tratamento, alérgenos, atopia, função pulmonar, início da asma e morte [HAN et al. 2010, JUST et al. 2017]. Atualmente, a maioria dos estudos de fenótipos da asma são feitos em adultos [YOUROUKOVA et al. 2017; KHUSIAL et al. 2017] e aqueles em crianças, foram realizados em países desenvolvidos [LEE et al. 2017; JUST et al. 2014; HOWRYLAK et al. 2014; FITZPATRICK et al. 2011]. Além disso, os fenótipos podem mudar conforme a população pesquisada. Por exemplo, Lee et al. (2017) mostraram que crianças sul-coreanas possuem fenótipos como a atopia e a gravidade da asma [LEE et al. 2017]. Já Just et al. (2014) mostraram que crianças americanas possuem diferentes fenótipos como o início precoce da asma, múltiplos alérgenos, a obesidade e a função pulmonar alterada [JUST et al. 2014]. Também em crianças americanas, Howrylak et al. (2014) mostram fenótipos classificados pelas variáveis atopia, histórico de exacerbação e grau de obstrução das vias aéreas [HOWRYLAK et al. 2014].

1.5 Obstrução das vias aéreas

A obstrução das vias aéreas é a limitação ao fluxo aéreo [GINA 2020]. Na asma, a obstrução das vias aéreas pode ser reversível espontaneamente ou com o tratamento; entretanto, algumas pessoas evoluem com obstrução fixa das vias aéreas (em inglês FAO) [TASHKIN et al. 2014]. A FAO é uma alteração estrutural do pulmão com limitação irreversível ao fluxo aéreo, mesmo após tratamento farmacológico [TASHKIN et al. 2014]. A FAO pode ser detectada ou pela relação $VEF_1/CVF < 0,8$ em crianças ou pela relação VEF_1/CVF menor que o limite inferior da normalidade (LIN) [GINA 2020; SWANNEY et al. 2008]. Embora ambas são usadas na prática clínica, a verificação pelo LIN reduz o erro de classificação da FAO [MAUREEN et al. 2008]. A melhor classificação pelo LIN é possível devido a uma equação que considera a idade, o sexo e a etnia [STANOJEVIC et al. 2010; GLI 2012].

Em geral, a FAO ocorre na fase adulta e uma recente revisão sistemática objetivou avaliar a FAO na asma e os autores verificaram apenas estudos em adultos [ZHANG et al. 2016]. A prevalência da FAO em adultos varia de 16 a 30% nas gravidades leve à moderada e pode chegar até 60% na asma grave [ZHANG et al. 2016; TASHKIN et al. 2016; TASHKIN et al. 2014]. Até onde temos conhecimento, existe apenas um estudo de FAO em jovens com idade média de 24 anos [LIMB et al. 2005], e nenhum em crianças e adolescentes. Pacientes com asma que desenvolvem a FAO tendem a ter asma mais grave, maior tempo de duração da doença, difícil controle da doença e menor resposta ao tratamento com corticoide inalatório e agonistas dos receptores adrenérgicos beta-2 [TASHKIN et al. 2014, ZHANG et al. 2016]. O motivo pelo qual a FAO ocorre

ainda é incerto. No entanto, a hipótese mais aceitável é que a FAO seja resultado do remodelamento das vias aéreas ao longo da vida [GUPTA et al. 2015].

1.6 Remodelamento brônquico

O remodelamento brônquico (RB) pode ser definido como processo de reorganização patológica da parede brônquica [NAYAK et al. 2018]. Investigações clínicas revelam que as mudanças estruturais da parede brônquica incluem: espessamento da via aérea, hiperplasia e hipertrofia da musculatura lisa, edema, fibrose epitelial, aumento da matriz extracelular e células imunes, acumulação de fibroblastos, angiogênese e hipersecreção [PRAKASH et al. 2017]. O espessamento das vias aéreas é uma das principais alterações histopatológicas do RB. Assim, ocorre mudanças fisiológicas na contração do músculo liso e perda da interdependência das vias aéreas [SHIFFREN et al. 2012, GUPTA et al. 2015]. A deterioração do pulmão pode afetar as vias aéreas de toda árvore brônquica e, conseqüentemente, limitação irreversível ao fluxo aéreo [NAYAK et al. 2018]. Dessa forma, os pacientes com RB apresentam função pulmonar alterada [BERAIR et al. 2017], maior sensação de dispneia e conseqüentemente menor nível de atividade física [FRANÇA-PINTO et al. 2015, WESTERGREN et al. 2017].

1.7 Atividade física e função pulmonar

A atividade física (AF) é definida como qualquer movimento corporal que resulte num gasto de energia acima do repouso [COLLEY et al. 2011]. A prática regular da AF traz benefícios musculares, esqueléticos, circulatórios e para a qualidade de vida de pessoas sem doenças crônicas [COLLEY et al. 2011].

Nesse sentido, os benefícios da AF também estão presentes no paciente com asma, sendo considerado um componente importante no programa de reabilitação pulmonar [EIJKEMANS et al. 2012]. Evidências sugerem que a prática regular do exercício físico reduz a hiperresponsividade brônquica [FRANÇA-PINTO et al. 2015], o uso do corticoide [FANELLI et al. 2007], o risco de exacerbação e hospitalização [EMTNER et al. 2016], as inflamações sistêmicas e da via aérea [FRANÇA-PINTO et al. 2015; MENDES et al. 2011], melhora os fatores de saúde relacionados à qualidade de vida [MENDES et al. 2010] e reduz a sensação de dispneia [CHANDRATILLEKE et al. 2012].

Apesar dos benefícios da AF na saúde geral de crianças e adolescentes [COLLEY et al. 2011], não existe um consenso dos efeitos da AF na função pulmonar nem de pessoas sem asma, nem naquelas com asma. Alguns estudos avaliam atletas de elite sem asma e mostram divergências nos resultados [TURMEL et al. 2012; RUBINI et al. 2016]. Turmel et al. (2012) mostrou não haver diferença no VEF_1 entre atletas de diferentes modalidades [TURMEL et al. 2012]. Por outro lado, Rubini et al. (2016) mostrou que adolescentes que praticam natação de provas longas apresentam maior VEF_1 do que aqueles que praticam provas curtas [RUBINI et al. 2016]. Os pesquisadores supõem que o aumento do VEF_1 pode acontecer devido ao padrão respiratório de repetidas apneias usado pelos nadadores durante as provas longas [RUBINI et al. 2016]. No entanto, a hipótese mais provável é que o aumento do VEF_1 nos adolescentes acontece devido ao desenvolvimento da caixa torácica e do pulmão [McGEACHIE et al. 2016].

O comportamento da função pulmonar no indivíduo com asma que pratica atividade física também mostra diferentes resultados [WANROOIJ et al. 2014; EICHENBERGER et al. 2013; TURMEL et al. 2012]. Uma revisão sistemática mostrou que o treinamento aeróbico não melhora parâmetros da função pulmonar, mas melhora discretamente o pico de fluxo expiratório [WANROOIJ et al. 2014]. Ao contrário, outra revisão mostrou que o VEF₁ basal melhora com o treinamento físico, porém o pico de fluxo expiratório se mantém inalterado [EICHENBERGER et al. 2013]. Como previamente exposto, não há evidências claras da melhora do VEF₁ com o treinamento físico, tanto em atletas como em pessoas com asma [WANROOIJ et al. 2014; TURMEL et al. 2012]. Existem evidências que indivíduos com queda da relação VEF₁/CVF e do VEF₁ apresentam limitação aos exercícios e baixa potência aeróbica [WESTERGREN et al. 2017; VILLA et al. 2011]. Além disso, alguns estudos comparam a AF em indivíduos de diferentes gravidades da asma e sem asma [SOUSA et al. 2014; VAHLKVIST et al. 2010; BERNTSEN et al. 2009]. Nesses estudos, indivíduos com asma praticam AF similar a aqueles sem asma [SOUSA et al. 2014; VAHLKVIST et al. 2010; BERNTSEN et al. 2009]. Esses dados sugerem que a gravidade da asma pode não limitar a prática regular da AF na infância. Entretanto, não se sabe como é o comportamento das variáveis físicas em adolescentes com função pulmonar alterada.

2. Justificativa

2.1 Estudo dos fenótipos

Estudos com o objetivo de avaliar fenótipos têm sido feitos para melhorar o manejo do tratamento da asma em países desenvolvidos; entretanto, pouco se sabe sobre os fenótipos clínicos de crianças e adolescentes com asma de países em desenvolvimento.

2.2 Estudo dos fatores de risco para o desenvolvimento da FAO

A obstrução fixa das vias aéreas (FAO) tem sido reportada como um dos fenótipos clínicos de pacientes com asma; entretanto, os estudos que avaliam a FAO na asma foram feitos em adultos. Na população infantil, a incidência, assim como os fatores de risco para o desenvolvimento da FAO permanecem desconhecidos.

2.3 Estudo da avaliação física na obstrução fixa das vias aéreas

A limitação ao fluxo aéreo aumenta a sensação de dispneia e consequentemente pode reduzir a prática regular da atividade física; entretanto, ainda nenhum estudo comparou o NAF, a potência aeróbia, a força muscular e a qualidade de vida em adolescentes com diagnóstico de asma com FAO e sem FAO.

3. Hipótese

3.1 Estudo dos fenótipos

Nossa hipótese é que os fenótipos das crianças e adolescentes com asma que residem em países em desenvolvimento possam ser diferentes dos fenótipos daquelas pessoas que residem em países desenvolvidos.

3.2 Estudo dos fatores de risco para o desenvolvimento da FAO

Nossa hipótese é que os fatores de risco para o desenvolvimento da FAO em crianças e adolescentes sejam diferentes daqueles previamente observados em adultos com asma.

3.3 Estudo da avaliação física na obstrução fixa das vias aéreas

Nossa hipótese é que adolescentes com FAO apresentam menor NAF, potencial aeróbico, força muscular e pior qualidade de vida quando comparado com pacientes sem FAO.

4. Objetivos

4.1 Estudos dos fenótipos

Identificar os fenótipos clínicos da asma em crianças e adolescentes que residem na cidade de São Paulo.

4.2 Estudo dos fatores de risco para o desenvolvimento da FAO

Identificar os fatores de risco para o desenvolvimento da obstrução fixa das vias aéreas em crianças e adolescentes com asma.

4.3 Estudo da avaliação física na obstrução fixa das vias aéreas

Avaliar e comparar o nível de atividade física, a potência aeróbia, força muscular respiratória e periférica e qualidade de vida de adolescentes portadores de asma com FAO e sem FAO.

5. Método

5.1 Pacientes

O projeto de pesquisa foi realizado em 2 fases. A 1ª fase teve 2 estudos: fenótipos clínicos e fatores de risco para o desenvolvimento da FAO em crianças e adolescentes com asma. Já a 2ª fase teve 1 estudo: avaliação física dos pacientes com FAO.

Os pacientes foram recrutados no ambulatório do Hospital Infantil Darcy Vargas (HIDV) localizado na cidade de São Paulo e os critérios de inclusão foram: ter diagnóstico de asma conforme a recomendação do GINA, idade entre 6 a 18 anos e estar em tratamento médico da asma, por pelo menos, 12 meses.

Foram excluídos aqueles pacientes que já tinham a FAO no início do estudo, abandono do tratamento da asma e ter menos de 3 visitas anuais ao ambulatório de asma. Ademais, pacientes com doenças cardíacas, neurológicas, hematológicas e osteomusculares também foram excluídos. O estudo foi aprovado pelo Comitê de Ética com protocolo 1540338.

5.2 Desenho dos estudos

O estudo dos fenótipos clínicos, fatores de risco para o desenvolvimento da FAO e avaliação física na FAO foram estudos retrospectivo, prospectivo e transversal, respectivamente.

O HIDV recebe pacientes da região metropolitana de São Paulo encaminhado pelos postos de saúde. Os pacientes chegaram ao hospital com histórico de sibilância, dispneia, aperto no peito ou cansaço ao esforço e então, o atendimento especializado era iniciado. Na primeira consulta no ambulatório médico de pneumologia, foi realizada uma avaliação completa e aqueles que aceitaram a participar do estudo assinaram o termo de consentimento livre e esclarecido, tiveram seus dados coletados e foram acompanhados pelos pesquisadores. Já os pacientes ou responsáveis que não aceitaram participar do estudo tiveram seu tratamento adequado garantido sem sofrer nenhum tipo de dano ou prejuízo. A continuidade do tratamento ocorreu por consultas pré-agendadas a cada 3 ou 4 meses durante os anos dos estudos. Em cada consulta, foi analisada o controle clínico da asma conforme *Childhood Asthma Control Test* (C-ACT), prova de função pulmonar, sintomas diurno e noturno da asma, limitação da atividade física e necessidade do uso de medicamento de resgate.

Para os pacientes que participaram da 2ª fase do estudo foram agendadas duas visitas. A primeira e a segunda visita foram no HIDV e Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), respectivamente. Na primeira visita, os pacientes realizaram os testes de força muscular inspiratória, expiratória, membros superiores e inferiores. Em seguida, receberam o acelerômetro (*Actigraph* GT3X), assim como as instruções para uso do aparelho. O início do uso do aparelho aconteceu ao acordar do dia seguinte a primeira visita e permaneceu por 7 dias consecutivos. Os participantes usam o acelerômetro no quadril anexado a cintura, retirando apenas para tomar banho

e dormir. A segunda visita ocorreu 8 dias após a primeira, onde o paciente devolveu o acelerômetro e realizou o teste de esforço cardiopulmonar (TECP) (Figura 1).

Figura 1: Fluxograma de visitas na 2ª fase. Avaliação da força muscular inspiratória, expiratória, membros superiores (MMSS) e inferiores (MMII), qualidade de vida, uso do acelerômetro e teste de esforço cardiopulmonar. TECP: teste de esforço cardiopulmonar.

5.3 Variáveis analisadas

5.3.1 Definição da obstrução fixa das vias aéreas

A FAO foi definida usando o resultado do teste de espirometria quando a relação do VEF_1/CVF após o broncodilatador era persistentemente menor que o limite inferior da normalidade (LIN) para a idade, sexo e altura [QUANJER et al. 2012]. Pacientes que apresentavam o VEF_1/CVF menor que o LIN por duas visitas consecutivas, iniciou tratamento com corticoide oral, dose de 1 a 2 miligramas por quilo de peso até a dose máxima de 40 miligramas por dia [GINA

2018]. Após 7 dias, o paciente retornou ao hospital e realizou novo teste de espirometria. Se o VEF₁/CVF permanecesse menor que o LIN, a presença da FAO era detectada [ESCHENBACHER 2016; SWANNEY et al. 2008].

5.3.2 Função pulmonar

A prova de função pulmonar foi feita antes e depois da inalação com 400 µg de salbutamol. O procedimento técnico, critérios de aceitabilidade e reprodutibilidade foram seguidos conforme *European Respiratory Society* e *American Thoracic Society* [PELLEGRINO et al. 2005]. As variáveis avaliadas foram VEF₁, CVF e relação VEF₁/CVF, sendo os valores preditos para a normalidade do teste conforme o estudo de Quanjer et al (2012) [QUANJER et al. 2012]. O equipamento usado foi o *Koko® PDS*, Ferraris, Louville, CO (EUA) acoplado ao microcomputador.

5.3.3 Gravidade da asma

Atualmente a gravidade da asma é classificada de 5 maneiras distintas: “steps” 1, 2, 3, 4 e 5, conforme o tipo e dose de corticosteroide usado pelo paciente [GINA 2020].

5.3.4 Controle da asma

O *Childhood Asthma Control Test* (C-ACT) trata-se de um questionário que avalia o controle da asma baseado nas últimas quatro semanas de vida, traduzido e validado para o português [ROXO et al. 2010]. O questionário é

composto por sete questões, sendo quatro para as crianças e três para os responsáveis. As perguntas para as crianças possuem quatro possíveis respostas, enquanto as perguntas para os responsáveis possuem seis possíveis respostas. A pontuação final varia de zero a vinte e sete, sendo que, quanto maior a pontuação, maior é o controle da asma. O controle da asma é considerado bom quando se atinge a pontuação ≥ 20 [LIU et al. 2007].

5.3.5 Início da asma

Foi verificado junto ao prontuário médico e aos cuidadores dos pacientes, a idade com que os sintomas da asma se iniciaram. A nota de corte de 2 anos de idade foi usada para definir asma de início precoce ou tardio [FERRY et al. 2014].

5.3.6 Exacerbações frequentes

A exacerbação frequente da asma foi considerada quando houve ≥ 3 episódios de exacerbações de asma em um período de 12 meses consecutivos, mesmo com o tratamento [WENZEL et al. 2008]. A duração das exacerbações foi contabilizada pelo tempo subsequente (em anos) que o paciente apresentou exacerbações frequentes.

5.3.7 Alergia

A alergia foi definida pelo do nível sérico de Imunoglobulina E (IgE) total e específico [BERNSTEIN et al. 2008]. A IgE total foi medida por meio do método de ensaio imunoenzimático [BERNSTEIN et al. 2008]. A alergia foi considerada

presente quando o IgE total era > 400 UI/mL. O teste de IgE específico foi feito pelo método fluoroenzimaimunoensaio e teve como ponto de corte 0,35KU/L. Se IgE específica fosse $\geq 0,35$ KU/L foi considerada alérgico ao alérgeno testado, caso $< 0,35$ KU/L foi considerado não alérgico [BURNEY et al. 1997]. A classificação de IgE específico varia de zero a seis, onde zero representa não haver alergia e seis representa o máximo de alergia ao alérgeno pesquisado [HOGAN et al. 2008, BURNEY et al. 1997].

5.3.8 Índice de Massa Corporal (IMC)

O IMC é uma medida indireta de gordura corporal e pode ser quantificado pela relação entre a massa corpórea em (kg), e pelo quadrado da altura em (m^2) e expresso como kg/m^2 . O percentil de IMC é um cálculo matemático que representa a posição relativa do IMC na criança e no adolescente perante os indivíduos do mesmo sexo e idade. Os valores de classificação estão representados no Anexo 2 [COLE e LOBSTEIN et al. 2012].

5.3.9 Avaliação do nível de atividade

O nível de atividade física foi avaliado pelo acelerômetro *Actigraph* GT3X (Anexo 4) e ajustado conforme peso, estatura e idade do adolescente. O aparelho mensura as atividades tri-axiais que fornecem medições da quantidade e intensidade da atividade física. Os dispositivos foram inicializados por computador e os dados coletados em *epoch* 15 segundos pelo *software* (*ActiLife* versão 6.9.5). Os pacientes usaram o dispositivo no quadril fixado a uma cinta por 7 dias consecutivos, incluindo dias da semana e fim de semana. Os dados foram apresentados em média de número de passos por dia, tempo gasto em

atividade física de intensidade leve, moderada e vigorosa [FREEDSON et al. 2005].

5.3.10 Teste de esforço cardiopulmonar

Os pacientes foram submetidos a um teste de esforço máximo utilizando um protocolo de exercício incremental de acordo com as diretrizes recomendadas pela *American Thoracic Society/American College of Chest Physicians* (2003). O TECP foi realizado numa bicicleta ergométrica (*Spinning Athletic Works modelo AW-3017D*) e contou com um período de aquecimento de 3 minutos, no qual os indivíduos pedalarão a uma velocidade de 50-60 rotação por minuto (rpm) sem carga. A partir daí, houve um aumento progressivo de carga de 15 Watts (W) a cada minuto para pacientes de até 150 centímetro (cm) de estatura e 20 W para aqueles acima de 150 cm de estatura, de forma que o teste de exercício durasse de 8 a 12 minutos, atingisse mais que 90% da frequência cardíaca máxima e coeficiente respiratório $\geq 1,10$ do previsto (WASSERMAN et al. 1999). Durante o teste, o paciente respirou por meio de um sensor de fluxo de via única para a coleta dos dados ventilatórios. A saturação de oxigênio, o eletrocardiograma e a pressão arterial sanguínea foram continuamente monitoradas. Dados como o consumo de oxigênio (VO_2), o volume minuto (VE), a produção de dióxido de carbono (VCO_2), o coeficiente respiratório (QR), as pressões de O_2 e CO_2 ao final da expiração (PETO_2 e PETCO_2), o volume corrente (VC), a frequência cardíaca máxima ($\text{FC}_{\text{máx}}$) e o pulso de oxigênio (PuO_2) foram as variáveis coletadas. O valor preditivo do VO_2 foi calculado de acordo com a equação de Ludwick (1983) [para o sexo masculino = $60 - (0,55 \times \text{idade})$ e para o feminino = $48 - (0,37 \times \text{idade})$]. O pico do VO_2 foi

usado para quantificar se os pacientes tinham bom potencial aeróbico, sendo a nota de corte $\geq 43,3$ e $\geq 35,6$ mL/kg/min, respectivamente meninos e meninas [RODRIGUES et al. 2006].

5.3.11 Força muscular respiratória

A força muscular respiratória foi avaliada pela pressão inspiratória (PI_{máx}) e expiratória (PE_{máx}) máxima, por meio do manovacuômetro (MVD300®). As medidas foram realizadas com o paciente sentado numa cadeira e solicitado a realização de um esforço inspiratório máximo a partir do volume residual para medir a PI_{máx}, e uma expiração forçada a partir da capacidade pulmonar total para medir a PE_{máx}. Foram realizadas 5 manobras com intervalo de 1 minuto entre as medidas e calculado a média dos 3 melhores valores com variabilidade menor que 5% [HEINZMANN-FILHO et al. 2016].

5.3.12 Força muscular periférica

A força muscular dos membros superiores e inferiores foram avaliados com dinamômetro Jamar Lafayette e EMG System, respectivamente. Foi solicitado que o paciente sustentasse uma força máxima de no mínimo 5 segundos com o membro dominante. Cada grupo muscular foi avaliado por 5 vezes com intervalo de 1 minuto entre os movimentos. Dos 5 movimentos, os 3 melhores resultados com variação menor que 5% foram considerados para calcular uma média [NOVAES et al. 2009].

5.3.13 Avaliação da qualidade de vida

A qualidade de vida foi avaliada pelo instrumento *Pediatric Asthma Quality of Life Questionnaire* (PAQLQ), traduzido e validado para o português do Brasil [LA SCALA et al. 2005]. O questionário é composto por 23 perguntas distribuídas em 3 domínios: sintomas (10 perguntas); limitação física (5 perguntas) e função emocional (8 perguntas). O questionário de qualidade de vida apresenta respostas de modelo *Likert*, sendo que cada pergunta possui 7 opções de escolha. O score varia de 1 a 7, sendo 1 pior e 7 melhor qualidade de vida. A pontuação total do questionário e dos domínios é a soma de cada questão dividida pelo número de perguntas [JUNIPER et al. 1996].

5.4 Análise estatística

A primeira fase da pesquisa foi composta por amostra de conveniência com os pacientes admitidos no HIDV e que preencheram os critérios de inclusão. A segunda fase foi composta por um cálculo amostral por meio do pico de consumo de oxigênio onde foi estimado 20 pacientes por grupo. O poder da amostra do teste foi estabelecido em 80% e o nível de significância ajustado para 5% ($p < 0,05$). Os dados foram analisados pelo programa *Statistical Package for Social Science* (SPSS), versão 17, 19 e 22 (Chicago, IL, EUA). A normalidade dos dados quantitativos foi analisada pelo teste de Kolmogorov-Smirnov. Para a comparação das variáveis quantitativas e categóricas de dados normais, foi usado o teste *t Student* e qui-quadrado, respectivamente; enquanto para os dados não normais foi usado o teste de *Mann–Whitney* e *Fisher*, respectivamente. Para a análise de agrupamento foi usado o teste de

aglomeração em duas etapas, além disso o critério *Bayesiano* de *Shwarz* foi usado para determinar o número de agrupamentos.

6. Resultados

6.1 Artigo: Fenótipos

Phenotypes of asthma in low-income children and adolescents: cluster analysis

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Submitted: 5 February 2016.

Accepted: 7 July 2016.

Study carried out at Hospital Infantil Darcy Vargas, São Paulo (SP) Brasil.

ABSTRACT

Objective: Studies characterizing asthma phenotypes have predominantly included adults or have involved children and adolescents in developed countries. Therefore, their applicability in other populations, such as those of developing countries, remains indeterminate. Our objective was to determine how low-income children and adolescents with asthma in Brazil are distributed across a cluster analysis. **Methods:** We included 306 children and adolescents (6-18 years of age) with a clinical diagnosis of asthma and under medical treatment for at least one year of follow-up. At enrollment, all the patients were clinically stable. For the cluster analysis, we selected 20 variables commonly measured in clinical practice and considered important in defining asthma phenotypes. Variables with high multicollinearity were excluded. A cluster analysis was applied using a two-step agglomerative test and log-likelihood distance measure. **Results:** Three clusters were defined for our population. Cluster 1 (n = 94) included subjects with normal pulmonary function, mild eosinophil inflammation, few exacerbations, later age at asthma onset, and mild atopy. Cluster 2 (n = 87) included those with normal pulmonary function, a moderate number of exacerbations, early age at asthma onset, more severe eosinophil inflammation, and moderate atopy. Cluster 3 (n = 108) included those with poor pulmonary function, frequent exacerbations, severe eosinophil inflammation, and severe atopy. **Conclusions:** Asthma was characterized by the presence of atopy, number of exacerbations, and lung function in low-income children and adolescents in Brazil. The many similarities with previous cluster analyses of phenotypes indicate that this approach shows good generalizability.

Keywords: Asthma/classification; Asthma/etiology; Child; Adolescent.

INTRODUCTION

Asthma is a syndrome of recurrent respiratory symptoms triggered by various factors, such as viral respiratory infections, environmental allergens, pollution, and climate changes. It is characterized by chronic airway inflammation and variable expiratory airflow limitation.⁽¹⁾ Asthma is not a single disease; rather, it comprises a syndrome with complex phenotypes. Various previous studies have attempted to subclassify asthma according to the symptoms, airway function, presence of atopy, and type of airway inflammation. Numerous asthma phenotypes have been described by using computational techniques, such as clustering; however, those studies predominately included adults,⁽²⁻⁴⁾ and the results suggested a weak correlation between pathological processes and treatment response.⁽¹⁾

Limited studies have focused on childhood asthma.⁽⁵⁻⁸⁾ Fitzpatrick et al.⁽⁶⁾ described four clusters in a group of 161 children and adolescents who primarily exhibited severe asthma; the obtained clusters were distinct from the clusters identified in adults because they were differentiated by the age at asthma onset, pulmonary

function, presence of atopy, airflow limitation, and comorbidity. Howrylak et al.⁽⁷⁾ described five clusters in a group of 1,041 children with mild-to-moderate asthma, which were differentiated by atopic burden, lung function, and history of exacerbation. Just et al.⁽⁸⁾ only investigated children with allergic asthma and described three clusters according to sensitization and presence of severe exacerbation.

According to the 2014 Global Initiative for Asthma (GINA) strategy report,⁽⁹⁾ the severity of asthma may be classified into five levels, and the key factors to determine asthma severity include symptom magnitude, pulmonary function, and dose of inhaled corticosteroid (ICS) to maintain asthma control. However, this classification does not reflect the heterogeneous characteristics of childhood asthma, which may lead to suboptimal treatments and increased risks of hospitalization, as well as loss of pulmonary function. For example, a great number of children and adolescents with severe asthma have normal lung function during symptom-free days, because FEV₁ does not correlate well with the symptoms; in addition, FEV₁ values lower than 80% are predicted

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Financial support: This study received financial support from Novartis S.A. and from the Brazilian Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, National Council for Scientific and Technological Development; Grant no. 311443/2014-1). Novartis played no role in the design, methods, data management, analysis, or in the decision to publish.

to have a low sensitivity to distinguish among the levels of asthma severity in children.⁽¹⁰⁻¹²⁾ Moreover, asthma symptoms vary in frequency and intensity through time and are triggered by various stimuli, such as viral infections and allergens. The reasons why some children exhibit only sporadic symptoms that are improved by short-acting bronchodilators and other children exhibit daily symptoms that require high doses of ICS and ongoing airway inflammation remain poorly understood.

Accurate asthma assessment is essential to avoid impairment and future risks of exacerbations, as well as to guide proper disease management.⁽¹⁾ Moreover, the identification of asthma phenotypes does not provide a better approach to asthma treatment, improve control, avoid adverse effects, or decrease the risk of serious asthma outcomes, such as exacerbations and loss of pulmonary function.⁽¹³⁾ This suggests the importance of additional studies in order to establish the actual clinical utility of phenotype classification. In addition, the previously described asthma phenotypes⁽⁶⁻⁸⁾ have been investigated in developed countries, and their applicability to other populations of children and adolescents with asthma remains to be established.

The purpose of the present study was to determine how low-income children with asthma in Brazil are distributed across a cluster analysis.

METHODS

This was a retrospective study involving 306 children and adolescents (6-18 years of age) with a clinical diagnosis of asthma who were outpatients at *Pinheiros Primary Care Unit* or at *Hospital Infantil Darcy Vargas*—both of which take part in the public health care system and are located in the city of São Paulo, Brazil—for at least one year of follow-up, between September of 2010 and December of 2014. Eligibility criteria were being between 6 and 18 years of age, a nonsmoker, and a representative of the community health care center. At enrollment, the participants were clinically stable with no signs of asthma exacerbation (30 days with no changes regarding symptoms or medication use). The severity of asthma was classified according to the revised 2014 GINA report,⁽⁹⁾ whereas asthma phenotypes were based on clinical data obtained from the medical records of the patients. The study was approved by the Research Ethics Committee of *Hospital Infantil Darcy Vargas* (Protocol no. 1.540.338). Since the present study was retrospective, the authors signed a confidentiality agreement which precluded the need to obtain written informed consent from the patients.

Selection of variables for analysis

The variables selected for the cluster analysis were considered important to define the disease phenotype and are commonly measured in clinical practice.⁽³⁻⁵⁾ Variables with high multicollinearity or that were similar for more than 95% of the patients were not included

in the cluster analysis. Twenty variables were included in the cluster analysis: gender (male or female); obesity (body mass index [BMI] ≥ 30 kg/m²); race (white, brown, or black); asthma severity based on prescribed treatment step (from 1 to 5)⁽⁹⁾; age at the onset of asthma (≤ 2 years, 3-6 years, or ≥ 7 years); asthma triggers (upper respiratory tract infection, exercise, or multiple triggers); blood eosinophils (absolute values and blood eosinophil levels $> 5\%$); number of previous asthma hospitalizations (none, 1-3, or ≥ 4); tendency toward exacerbation—more than 3 exacerbations in the previous year—(yes or no); history of ICU admission (yes or no); specific serum IgE levels (via ImmunoCAP Specific IgE; Phadia, Uppsala, Sweden)—atopy identified to most common allergens—(none, dust mite allergens, or multiple allergens); gastroesophageal reflux (yes or no); sinus infection (yes or no); baseline FEV₁ (% predicted); FEV₁/FVC ratio; labile FEV₁—defined as a variation in pre-bronchodilator FEV₁ $> 20\%$ between visits in the previous year—(yes or no); presence of fixed airway obstruction—persistence of post-bronchodilator airway obstruction or FEV₁/FVC ratio lower than the lower limit of normality⁽¹⁴⁾ despite the use of high doses of ICS and a 7-day course of prednisone—(yes or no); and best response to bronchodilator in the previous year.

Spirometric criteria were in accordance with Pellegrino et al.,⁽¹⁵⁾ and the tests were performed with a Koko® spirometer (PDS Instrumentation Inc., Louisville, CO, USA). Bronchodilator reversibility tests were performed using 400 µg of albuterol. Predictive values were in accordance with those proposed by Quanjer et al.⁽¹⁴⁾ Fixed airway obstruction was defined by lower limit of normal, which was based on the proportion of subjects in the groups whose test results fell below the fifth percentile, in accordance with the multiethnic reference values proposed by Quanjer et al.⁽¹⁴⁾

Statistical analysis

A uniform cluster analysis methodology was applied using an agglomerative two-step test and log-likelihood distance measure. The lowest Schwarz Bayesian information criterion was used to determine the number of clusters. This analytical technique identifies subgroups of a sample according to their similarities, which subsequently enables the determination of the variables that best discriminate such subgroups of the group a priori.⁽³⁾ To compare differences between the clusters, one-way ANOVA and chi-square tests were used for parametric continuous and categorical variables, respectively. A forward stepwise discriminant analysis using Wilks' lambda and Fisher's linear discriminant function was performed. A discriminant analysis was applied to identify factors that independently discriminate pre-specified groups and determined whether the subjects assigned to one group were different from the subjects assigned to another group. The dependent variable included cluster classification; the independent variables included the same 20 variables used in the cluster

analysis. A second discriminant analysis was conducted for asthma severity based on prescribed treatment step (from 1 to 5) as the dependent variable and the 20 variables included in the initial analysis as the independent variables. The present study included 15 subjects per variable, which is three times higher than the minimum recommendation for discriminant analysis (five subjects per variable).⁽¹⁶⁾ The statistical significance level was set at 5% for all tests. The IBM SPSS Statistics software package, version 19.0 (IBM Corporation, Armonk, NY, USA), was used for statistical analyses.

RESULTS

The clinical data regarding the 306 children and adolescents with asthma included in the study were available for the cluster analysis. Seventeen subjects were excluded due to incomplete data. The baseline characteristics of the remaining 289 subjects are presented in Table 1. In the sample studied, 177 subjects (61%) were male, the mean age was 12 years, and the vast majority exhibited atopic asthma (92%). The age at the onset of asthma in most subjects was < 2 years (68%); in addition, most were White (66%). Rhinitis and topic eczema were detected in 281

(97%) and in 13 (5%) of the patients, respectively. The sample was representative of the children and adolescents in the community who attended the public health care facilities. As for the severity of asthma, 107 subjects (35%) were classified as having mild asthma (steps 1 and 2), whereas 88 (29%) and 110 (36%) as having moderate asthma (step 3) and severe asthma (steps 4 and 5), respectively. Mean pulmonary function test results showed normal values; FEV₁ in % of predicted was 97.2% ± 12.3%, and FEV₁/FVC ratio was 0.86 ± 0.08.

Phenotypic characterization of asthma clusters

Table 2 shows the distribution of patients and the variables studied among the clusters. Cluster 1 (normal pulmonary function test results, mild eosinophilic inflammation, low tendency toward exacerbation, asthma onset at a later age, and mild atopy) included 94 (33%) of the subjects; they were equally distributed by gender (53%), and most were identified as having mild asthma (64% in steps 1 or 2) and mild eosinophilic inflammation (blood eosinophil levels > 5% in 37% of the subjects). Cluster 1 exhibited the lowest tendency toward exacerbation—66% had had no hospitalizations due to asthma in the previous year,

Table 1. Baseline characteristics of the children and adolescents with asthma stratified by asthma severity.^a

Characteristic	Asthma severity			Total	p
	Mild (steps 1-2)	Moderate (step 3)	Severe (steps 4-5)		
Number of subjects	100	84	105	289	
Anthropometric data					
Male	60 (60)	44 (52)	73 (70)	177 (61)	0.05
Age, years	12 ± 3	13 ± 4	12 ± 3	12 ± 3	0.44
BMI, kg/m ²	19.9 ± 4.1	20.2 ± 4.2	19.8 ± 4.2	19.9 ± 4.2	0.81
Obesity	13 (13)	10 (12)	9 (9)	32 (11)	0.57
Race					
White	66 (66)	57 (68)	66 (63)	190 (66)	0.93
Brown	30 (30)	25 (30)	35 (33)	90 (31)	
Black	4 (4)	2 (2)	4 (4)	10 (3)	
Age at asthma onset, years					
≤ 2	67 (67)	59 (70)	72 (69)	199 (69)	0.18
3-6	21 (21)	17 (20)	21 (20)	59 (20)	
≥ 7	12 (12)	8 (9)	12 (11)	32 (11)	
Atopy	89 (89)	76 (89)	100 (95)	265 (92)	0.41
Pulmonary function					
FEV ₁ , % predicted	100.2 ± 12.0	97.5 ± 11.6	94.5 ± 13.1	97.2 ± 12.3	0.32
FEV ₁ /FVC	0.88 ± 0.06	0.85 ± 0.08	0.85 ± 0.09	0.86 ± 0.08	0.03
Fixed airway obstruction	8 (8)	12 (14)	18 (17)	38 (13)	0.14
Bronchodilator response	17.5 ± 9.3	20.1 ± 11.4	22.9 ± 16.6	20.2 ± 13.1	0.01
Hospitalization due to asthma in the previous year					
None	56 (56)	48 (57)	57 (45)	151 (52)	0.31
1-3	24 (24)	21 (25)	28 (27)	73 (25)	
≥ 4	20 (20)	15 (18)	30 (27)	66 (23)	
Exacerbation tendency	36 (36)	40 (48)	43 (41)	119 (41)	0.28
Hospitalization in an ICU	7 (7)	6 (7)	13 (12)	26 (9)	0.31

BMI: body mass index. ^aValues expressed as n (%) or mean ± SD.

30% showed a tendency toward exacerbation, and 5% had a history of ICU admission. Atopy was less common in cluster 1 subjects than in those in the other clusters (negative tests for specific serum IgE in 16% and mean total IgE = 721.1 ± 682.3 IU/mL). The pulmonary function was characterized by showing the highest values for pre- and post-bronchodilator FEV₁ (% of predicted) and for the FEV₁/FVC ratio. Labile bronchodilator response (mean FEV₁ = $16.5\% \pm 9.5\%$ of predicted) and fixed airway obstruction were the lowest among the clusters, whereas the age at asthma onset was the highest (≥ 7 years of age in 19%).

Cluster 2 (normal pulmonary function test results, severe eosinophilic inflammation, severe atopy, high tendency for exacerbation, and early age at asthma onset) comprised the smallest number of subjects ($n = 87$; 30%). It primarily comprised male subjects (56%) with moderate asthma (step 3; 47%), increased blood eosinophilic inflammation (blood eosinophil levels $> 5\%$ in 98%), and increased IgE (mean = $1,361.6 \pm 1,137.8$ IU/mL). The specific serum IgE test was primarily positive for mites (37%), and upper respiratory tract infection was the most relevant asthma trigger (70%). Health care utilization in the previous year ranged between that in clusters 1 and 3; however, the tendency toward exacerbation was the highest (58%). Pulmonary function was predominantly normal; only 4 (5%) of the patients were diagnosed with fixed airway obstruction. Moreover, most of the subjects in cluster 2 had an early age at asthma onset (< 2 years in 77%).

Cluster 3 (poor pulmonary function test results, severe eosinophilic inflammation, severe atopy, and high tendency for exacerbation) comprised the largest group ($n = 108$; 37%). This cluster exhibited the highest proportion of male subjects (72%), with predominately severe asthma (step 4 or 5 in 54%), increased eosinophilic inflammation (eosinophil levels $> 5\%$ in 86%), and high IgE levels (mean = $1,222.6 \pm 973.0$ IU/mL). The specific serum IgE test was predominantly positive for multiple factors (90%), and the majority presented multiple asthma triggers (74%). The subjects in cluster 3 exhibited a greater number of exacerbations than did those in the other clusters (hospitalizations due to asthma in the previous year in 64% and history of ICU admission in 16%). The subjects in cluster 3 had the worst pulmonary function test results (the lowest pre- and post-bronchodilator FEV₁ in % of predicted and FEV₁/FVC ratio). Moreover, those subjects most often showed fixed airway obstruction, labile VEF₁, and poor bronchodilator responses than did those in the other clusters.

Discriminant analysis

The multiple discriminant analysis using the same 20 variables included in the cluster analysis indicated that 10 variables strongly discriminated the cluster:

atopic burden (blood eosinophil levels and specific serum IgE test), pulmonary function (fixed airway obstruction, labile FEV₁, and poor bronchodilator response), health care utilization (tendency toward exacerbation and hospitalization in the previous year), asthma triggers, asthma severity, and age at onset of asthma. The discriminant function model exhibited good accuracy and predicted 90% of the case allocations correctly. The second discriminant analysis, in which asthma severity (prescribed treatment step 1, 2, 3, 4, or 5) was used as a dependent variable exhibited poor accuracy and predicted only 31% of the case allocations correctly.

DISCUSSION

Asthma in children and adolescents is a complicated and heterogeneous disorder with distinct phenotypes. We identified three clusters by using an unsupervised cluster analysis in low-income children and adolescents with a wide range of levels of asthma severity. In cluster 1, there were less frequent health care utilization, milder atopy, older age at asthma onset, milder asthma, and normal lung function. The patients in cluster 2 showed normal pulmonary function test results, more severe eosinophilic inflammation, more severe atopy status, a moderate number of exacerbations, and asthma onset at an earlier age. Finally, the patients in cluster 3 presented with poor pulmonary function, severe eosinophilic inflammation, severe atopy status, and high number of exacerbations.

The demographic characteristics of our patients are consistent with childhood asthma, the characteristics of which include a higher proportion of boys, early age at asthma onset, and there are presence of atopy and a high prevalence of rhinitis. The coexistence of atopy, rhinitis, and asthma has also been previously observed in a cross-sectional study including children with asthma.⁽¹⁷⁾ The authors suggested that asthma, rhinitis, and eczema can be classified altogether as an allergic comorbidity.

The cluster analysis indicated only three clusters of children and adolescents with shared phenotypic characteristics, whereas Fitzpatrick et al.⁽⁶⁾ described four clusters, and Howrylak et al.⁽⁷⁾ described five clusters. The characteristics that differentiated each cluster were similar to the characteristics reported in previous studies^(6,7,18); the common characteristics among the current and the previous studies included atopic burden, lung function, and health care utilization. However, the age at the onset of asthma in our study was a distinguishing feature when we compare it with the study by Fitzpatrick et al.⁽⁶⁾ The clusters previously reported exhibited more heterogeneous clinical features when compared with those in the present study, which was grouped into only three clusters. We also observed that there was an association of a high proportion of patients with allergy due to multiple factors with poorer pulmonary function, severe asthma, more severe eosinophilic

Table 2. Characteristics of the children and adolescents with asthma stratified by cluster analysis.^a

Characteristic	All	Cluster 1	Cluster 2	Cluster 3	p
Number of subjects	289	94	87	108	
Anthropometric data					
Male	177 (61)	50 (53)	49 (56)	78 (72)	0.01
Age, years	12 (3)	11 (4)	12 (3)	13 (3)	0.04
BMI, kg/m ²	19.9 ± 4.2	19.4 ± 3.5	19.6 ± 4.0	20.6 ± 4.0	0.10
Obesity	32 (11)	11 (12)	8 (9)	13 (12)	0.79
Race					0.06
White	190 (66)	59 (63)	54 (62)	76 (70)	
Brown	90 (31)	35 (37)	27 (31)	28 (25)	
Black	10 (3)	0 (0)	6 (7)	4 (4)	
Asthma severity, step					< 0.001
1	74 (25)	47 (50)	2 (2)	25 (23)	
2	26 (9)	13 (14)	12 (14)	1 (1)	
3	84 (29)	19 (20)	41 (47)	24 (22)	
4	98 (34)	13 (14)	31 (36)	53 (49)	
5	8 (3)	2 (2)	1 (1)	5 (5)	
Age at asthma onset, years					< 0.001
≤ 2	199 (69)	52 (55)	67 (77)	79 (73)	
3-6	59 (20)	24 (25)	20 (23)	15 (14)	
≥ 7	32 (11)	18 (19)	0 (0)	14 (13)	
Asthma triggers					< 0.001
URTI	138 (48)	53 (56)	61 (70)	24 (22)	
Exercise	23 (8)	8 (8)	11 (12)	4 (4)	
Multiple	129 (44)	33 (35)	15 (17)	80 (74)	
Hospitalization due to asthma in the previous year					< 0.001
None	151 (52)	62 (66)	50 (57)	39 (36)	
1-3	73 (25)	19 (20)	22 (25)	32 (30)	
≥ 4	66 (23)	13 (14)	15 (17)	37 (34)	
Exacerbation tendency	119 (41)	28 (30)	51 (58)	40 (37)	< 0.001
Hospitalization in an ICU	26 (9)	5 (5)	4 (5)	17 (16)	< 0.01
Atopic status					
IgE, IU/mL	1101.3 ± 980.7	721.1 ± 682.3	1361.6 ± 1137.8	1222.6 ± 973.0	< 0.001
Specific serum IgE test results					< 0.001
Negative	25 (9)	15 (16)	9 (10)	1 (1)	
Mites	61 (21)	18 (19)	32 (37)	11 (10)	
Multiple	204 (70)	61 (65)	46 (53)	96 (89)	
Blood eosinophils	8.1 ± 5.0	4.3 ± 3.1	10.6 ± 4.7	9.4 ± 4.8	< 0.001
Blood eosinophils > 5%	214 (74)	35 (37)	85 (98)	93 (86)	< 0.001
Reported comorbidities					
Allergic rhinitis	281 (97)	91 (97)	86 (99)	103 (95)	0.38
Topic eczema	13 (5)	4 (4)	3 (3)	6 (6)	0.77
Reflux	18 (6)	5 (5)	3 (3)	10 (9)	0.22
Bronchiectasis	6 (2)	2 (2)	2 (2)	2 (2)	0.97
Sinus infection	19 (7)	7 (7)	4 (5)	8 (7)	0.67
Pulmonary function					
Pre-BD FEV ₁ , % predicted	97.2 ± 12.3	102.1 ± 9.7	97.7 ± 13.9	92.9 ± 12.3	< 0.05
Post-BD FEV ₁ , % predicted	104.3 ± 13.3	108.8 ± 10.5	106.1 ± 15.4	98.5 ± 10.2	< 0.05
FEV ₁ /FVC	0.86 ± 0.08	0.90 ± 0.05	0.86 ± 0.06	0.82 ± 0.09	< 0.001
FEV ₁ lability ^b	160 (55)	31 (33)	40 (46)	89 (82)	< 0.001
Fixed airway obstruction	38 (13)	1 (1)	4 (5)	33 (31)	< 0.001
Bronchodilator response	20.2 ± 13.1	14.3 ± 8.2	18.0 ± 9.7	27.2 ± 15.6	< 0.001

BMI: body mass index; URTI: upper respiratory tract infection; and BD: bronchodilator. ^aValues expressed as n (%) or mean ± SD. ^bVariation > 20% in pre-BD FEV₁ in one year.

inflammation, and a higher number of exacerbations. These findings are supported by a previous study demonstrating that patients presenting multiple allergy sensitizations also had a higher level of severity (moderate to severe asthma), a greater proportion of asthma exacerbations, and a significantly greater proportion of inflammatory markers.⁽⁸⁾

In our study, the discriminant analysis that used asthma severity as the dependent variable exhibited poor accuracy and predicted only 31% of the case allocations correctly. Moreover, only the FEV₁/FVC ratio and the response to bronchodilators were significantly different among the groups. Health care utilization and fixed airway obstruction were not distinguishing features of asthma severity. Similarly to other studies involving children⁽⁶⁻⁸⁾ or adults,⁽²⁻⁴⁾ the asthma phenotypes did not correspond to the levels of asthma severity proposed by the GINA guidelines.⁽⁹⁾ Moreover, asthma exacerbations and different levels of asthma severity were identified in all of the clusters, a finding that corroborates the study by Fitzpatrick et al.⁽⁶⁾ Despite few asthma symptoms and normal lung function, children with asthma also had severe exacerbations. For example, even children and adolescents with mild asthma reported ICU admissions. These findings might have occurred because of the poor socioeconomic conditions in our population; sometimes it is difficult for them to receive proper medical treatment during their infrequent asthma

exacerbations, which might worsen their respiratory status and lead them to an ICU.

The degree of pulmonary function impairment in children and adolescents is significantly lower than that previously observed in adults. Although fixed airway obstruction was more frequently found in the patients in cluster 3, it was also identified in those in the other two clusters (13% of the subjects). Therefore, spirometry alone is not a good parameter to determine asthma severity, and the use of spirometry for the management of childhood asthma seems not to improve, by itself, the quality of life of the patients.⁽¹⁹⁾ Most patients (87%) had no fixed airway obstruction, and this fact may present a window of opportunity for proper treatment.

In our population, we did not identify an association between obesity and asthma severity, as previously reported in adults.⁽²⁰⁾

In summary, childhood asthma is characterized by the presence of atopy, a high rate of exacerbations, and fairly preserved lung function. We identified various similarities with the previous clusters that had been described in children and adolescents, and this indicates that this approach has good generalizability. Our study might contribute to a better understanding of asthma phenotypes due to the lack of studies investigating asthma phenotypes in low-income children and adolescents.

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6.2 Artigo: Fatores de risco para o desenvolvimento da obstrução fixa das vias aéreas

ORIGINAL ARTICLE

Risk factors for fixed airflow obstruction in children and adolescents with asthma: 4-Year follow-up

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Funding information

Fundação de Amparo à Pesquisa do Estado de São Paulo, Grant/Award Number: 2016/05968-1; Coordenação de Aperfeiçoamento de Pessoal de Nível Superior-Brasil (CAPES)-Finance Code 001; Conselho Nacional de Desenvolvimento Científico e Tecnológico, Grant/Award Number: 312.279/2018

Abstract

Background: Asthma is a disease with reversible bronchoconstriction; however, some patients develop fixed airflow obstruction (FAO). Previous studies have reported the incidence and risk factors of FAO in adults; however, the corresponding factors in children remain poorly understood.

Aim: To evaluate the incidence and risk factors of FAO in children and adolescents with asthma.

Method: Observational and prospective cohort study with a 4-year follow-up of clinically stable patients with asthma (from 6-8 years old). Anthropometric data, history of asthma, number of hospitalizations, frequent exacerbations, asthma severity, asthma control, inhaled corticosteroid dose, atopy, and lung function were analyzed as potential risk factors for FAO. FAO was defined by a ratio of the forced expiratory volume in the first second to the forced vital capacity below the lower limit of normal, even after inhaled and oral corticosteroid treatment.

Results: Four hundred and twenty-eight patients were recruited, and 358 were analyzed. The FAO incidence in children and adolescents with asthma was 9.5% ($n = 34$), starting at 10 years of age. Age, body mass index, hospitalizations for asthma, bronchodilator response, frequent exacerbations, length of exacerbations, and asthma severity were associated with FAO. Frequent exacerbations (odds ratio [OR] = 4.0; 95% confidence interval [CI] = 1.3-11.7) and asthma severity categorized as steps 4 to 5 (OR = 3.5; 95% CI = 1.6-7.6) remained risk factors.

Conclusions: Frequent exacerbations and asthma severity are the risk factors for FAO in children and adolescents with asthma.

KEYWORDS

asthma phenotype, disease, exacerbation, hospitalization, lung function

1 | INTRODUCTION

Asthma is a chronic disease characterized by airway inflammation, and it is defined by a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness and coughing as well as variable airflow obstruction.¹ The symptoms and airflow obstruction can often be reversed either spontaneously or with

pharmacological treatment.² However, some patients with asthma demonstrate an expiratory airflow limitation that is not completely reversible despite optimal treatment; this condition is known as fixed airflow obstruction (FAO).³⁻⁵

FAO has been defined as a reduction in the forced expiratory volume in 1st second to forced vital capacity (FEV₁/FVC) ratio after bronchodilator (BD) use.^{4,6} Formerly, FAO was evaluated as an

FEV₁/FVC ratio lower than the fixed cut-offs of 0.7 and 0.8 in adults and children, respectively⁷; however, Swanney et al⁶ proposed a cut off based on the lower limit of normal (LLN). Some studies have demonstrated that the LLN definition may reduce the misclassification of FAO because the LLN value is derived from reference equations specific to every population and takes into account age, sex, and ethnicity.^{6,7}

A recent systematic review evaluated that the risk factors for FAO development in adults with asthma include male sex, onset of asthma in adulthood, frequent exacerbations, disease severity, poor lung function, airway inflammation, use of rescue medication, and smoking or exposure to pollution.⁵ This systematic review included one study with children and adolescents; however, the FAO was not evaluated until the early adult age (around 26 years old).⁸ Other studies have evaluated the patterns of lung function in childhood.^{9–15} These studies suggested that patients with asthma may present abnormal patterns of lung function; however, none of them have evaluated FAO. FAO is an important subject because it is associated with mortality in adulthood^{9,11,14} and its early detection can avoid lung function deterioration.

To the best of our knowledge, none of these previous studies evaluated the incidence and risk factors of FAO in children and adolescents. Thus, the present study aims to evaluate the incidence and risk factors of FAO in children and adolescents with asthma.

2 | METHODS

2.1 | Participants

This prospective cohort study with a 4-year follow-up was conducted with outpatient children and adolescents of both sexes who had asthma and were between 6 and 18 years of age. The study was conducted in a tertiary University Hospital with patients referred from general practices. Asthma was diagnosed in accordance with the Global Initiative for Asthma (GINA).¹⁶ The inclusion criteria were medical treatment for at least 12 months with inhaled corticosteroids according to the GINA guidelines¹⁶ and preserved lung function (an FEV₁/FVC ratio greater than the LLN).¹⁷ The exclusion criteria were discontinued asthma treatment, less than three annual medical visits, and the presence of any other diseases (Figure 1). The Hospital Ethics Research Committee approved the study and written informed consent was obtained from the children's caregivers. No financial compensation was offered for participation in the study.

2.2 | Study design

In the first visit, all patients were examined by a pulmonologist who performed a clinical examination, blood and spirometry tests and collected the asthma history. Asthma treatment with inhaled corticosteroids and short-acting β_2 -agonist or long-acting β_2 -agonist was prescribed and initiated based on symptom intensity and the spirometry test

results.¹⁶ During the 4-year follow-up, patients completed three to four hospital visits per year; a clinical examination and spirometry tests were performed during every visit. The medication dose was readjusted based on the treatment response, if necessary.¹⁶

2.3 | Outcomes

2.3.1 | FAO definition

FAO was defined using spirometry test results when the FEV₁/FVC ratio after BD use was persistently lower than the LLN from reference equations.⁴ In our study, if patients presented with an FEV₁/FVC ratio lower than the LLN after two consecutive visits, oral corticosteroids (OC) were prescribed for seven consecutive days (OC dose ranged from 1 to 2 milligrams per kg of body weight up to a maximum dose of 40 mg/day).¹ After 7 days of OC treatment, the patient returned to the hospital and underwent a new spirometry test. If the FEV₁/FVC ratio remained lower than the LLN,¹⁷ the presence of FAO was considered.⁶

2.4 | Clinical evaluation

2.4.1 | Body mass index

Body mass index (BMI) was calculated by dividing the patients' weight in kilograms by their heights in square meters (kg/m²).¹⁸ The weight status categories were underweight (<5th), normal weight (5th to <85th), overweight (85th to <95th), and obese ($\geq$ 95th).¹⁹

2.4.2 | Lung function test

Lung function was evaluated by a spirometer (Koko DigiDoser, Louisville, Kentucky), and the technical procedures and

FIGURE 1 STROBE diagram of the study patients. FAO, fixed airflow obstruction; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology

reproducibility were established as recommended by the American Thoracic Society/European Respiratory Society.²⁰ Spirometry was performed before and after the inhalation of 400 µg salbutamol, approximately 10 to 15 minutes apart to evaluate the BD response.²¹ A positive BD response was considered as previously described.²⁰ Predicted values were obtained from the Brazilian population,²¹ and the LLN was evaluated through a program provided by the Global Lung Initiative.²²

2.4.3 | Asthma severity

In 2012 and 2013, asthma severity was classified as intermittent or mild, moderate, or severe persistent.¹⁶ In 2014, the asthma severity classification was modified and categorized into five steps considering the type and dose of corticosteroid. Then, the patients included in 2012 and 2013 were reclassified according to this new classification.²³

2.4.4 | Asthma control

The Childhood Asthma Control Test (C-ACT) was used to assess asthma control.^{24,25} The C-ACT scores range from 0 (totally uncontrolled asthma) to 27 (totally controlled asthma), and scores ≥ 20 represent good asthma control.²⁴

2.4.5 | Onset of asthma

Early-onset asthma was defined as asthma symptoms beginning before the patient's second birthday, as previously described.²⁶

2.4.6 | Frequent exacerbations

An exacerbation was defined as acute episodes of increased symptoms and deteriorations in lung function requiring OC treatment.¹⁶ Patients who had ≥ 3 episodes of asthma exacerbation during 12 months at any point in their life were considered to have frequent exacerbations.²⁷

2.4.7 | Length of exacerbations

The number of consecutive years during life when exacerbations occurred.

2.4.8 | Allergies

Allergic responses were measured by serum immunoglobulin E (IgE) levels and eosinophil blood counts. Total IgE was measured with the

immunoenzymatic assay method, and the presence of an allergic reaction was considered when the total IgE was >400 IU/mL. The specific IgE test was conducted by using the Phadiatop method (Phadia 100; Thermo-Scientific, Phadia AB, Uppsala, Sweden), and a positive result was considered when the specific IgE levels were ≥ 0.35 kUA.²⁸ The eosinophils were measured by eosinophil counts in blood, and eosinophilic asthma was defined as a blood eosinophil count greater than or equal to 500 cells/ μ L.²⁸

2.5 | Statistical analysis

The data were analyzed using the Statistical Package for Social Science software, version 17.0 (Chicago, IL). The test power was set at 80%, and the significance level was adjusted to 5% ($P < .05$). The sample was composed of all patients who were admitted to the outpatient hospital and fulfilled the inclusion criteria (convenience sample). Data normality was analyzed by the Kolmogorov-Smirnov test. FAO was the dependent variable, and comparisons between the FAO and non-FAO groups were made using the Student *t* tests or the χ^2 test. Simple logistic regression and multiple logistic regression were used to estimate the crude and adjusted relative risks (RRs), respectively. The asthma severity variable was analyzed in three categories: steps 1 to 2, step 3, and steps 4 to 5. BMI was analyzed in two categories: under or normal weight and overweight or obese.

3 | RESULTS

A total of 428 children and adolescents were screened, and 70 were excluded, mostly (60%) because they either discontinued their asthma treatment or had fewer than three annual medical visits. The other reasons were as follows: diagnosis of another pulmonary disease; declined to participate; and FAO diagnosis in the first medical visit followed by a diagnosis of either cardiovascular or neurological disease (Figure 1). Three hundred fifty-eight patients completed the 4-year follow-up.

The patients were predominantly males of normal weight whose asthma severity was in category 1 or 2 and had high blood eosinophil counts and IgE levels (Table 1). The FAO group was older, had higher BMIs, had asthma severity in the steps 4 to 5 category, and had higher budesonide consumption than the non-FAO group. In addition, more patients in the FAO group reported frequent exacerbations than those in the non-FAO group, and the FAO group had a longer length of exacerbations and more hospitalizations than the non-FAO group ($P < .05$; Table 1). There were no differences in other pulmonary diseases, sex, C-ACT score, asthma onset age, atopy, or blood eosinophils between the groups (FAO and non-FAO) ($P > .05$; Table 1).

During the 4-year follow-up, 34 (9.5%) children and adolescents developed FAO (FEV₁/FVC ratio $<$ LLN), being higher in asthma categorized as steps 4 to 5 ($P < .05$; Figure 2). Twenty-one children and adolescents presented a temporary airflow obstruction (reduced

TABLE 1 Comparison of anthropometric data, allergic markers, and characteristics of asthma at study onset between the FAO and non-FAO groups

	All n = 358	FAO n = 34	non-FAO n = 324	P value
Anthropometric data				
Male (%)	212 (59.2%)	22 (65%)	190 (59%)	.49
Age, y	10.1 ± 3.6	12.1 ± 3.1	9.8 ± 3.6	<.001
BMI (percentile)	50.2 ± 36.1	62.4 ± 32.2	49.5 ± 37.5	.05
Weight status (%)				
Normal weight	294 (82%)	22 (65%)	272 (84%)	.001
Overweight/obese	64 (18%)	12 (35%)	52 (16%)	
Allergic markers				
Eosinophils, %	8.1 ± 4.9	8.1 ± 5.2	8.1 ± 4.9	.92
IgE total, U/mL	1,161 ± 1,105	1,415 ± 1,132	1,135 ± 1,101	.16
Number of allergens	2 ± 1	2.2 ± 0.9	1.9 ± 1	.1
Characteristic of asthma				
Asthma severity (%)				
Steps 1-2	161 (45)	9 (26.5)	152 (46.9)	
Step 3	130 (36.3)	8 (23.5)	122 (37.7)	
Steps 4-5*	67 (18.7)	17 (50)	50 (15.4)	<.001
Budesonide-equivalent dose	441 ± 227	607 ± 227	422 ± 219	<.001
Asthma control test	22.6 ± 2.8	22.2 ± 3.1	22.8 ± 2.7	.22
Onset asthma (%)				
Early, <2 y old	216 (60)	25 (73.5)	191 (59)	.09
Late, ≥2 y old	142 (40)	9 (26.5)	133 (41)	
Frequent exacerbations (%)				
Yes	227 (63.5)	29 (85)	198 (61)	.009
No	131 (36.5)	5 (15)	126 (39)	
Age of frequent exacerbations, y	5.9 ± 3.5	6.25 ± 4.3	5.8 ± 3.3	.66
Length of exacerbations, y	3.7 ± 3.4	4.3 ± 3.8	2.7 ± 2.5	<.001
Hospitalization (%)				
Yes	201 (56.2)	271 (75.7)	194 (54.1)	<.001
No	157 (43.8)	87 (24.3)	164 (45.9)	

Note: Data are presented as the means and standard deviations or percentages. χ^2 tests and the Student *t* tests were used to compare categorical and continuous variables, respectively. Patient with BMI percentiles from 5th to 84th and ≥85th were considered normal weight and overweight/obese, respectively. Asthma severity steps were considered according to GINA guidelines. Frequent exacerbations were considered ≥3 episodes of asthma requiring OC treatment in the previous 12 months.

Abbreviations: BMI, body mass index; FAO, fixed airflow obstruction; GINA, Global Initiative for Asthma; IgE, immunoglobulin E; OC, oral corticosteroid.

**P* < .001 compared FAO to non-FAO.

FEV₁/FVC ratio) that was reversed after 7 days of OC treatment; however, these participants were not included in the FAO group.

At baseline, patients from the FAO and non-FAO groups had similar pre- and post-BD lung function parameters (FEV₁/FVC ratio, FVC and FEV_{1%} of predicted) (*P* > .05; Table 2). After the 4-year follow-up, the FEV₁ and FEV₁/FVC ratio were lower in the FAO group than in the non-FAO group (*P* < .05; Table 2). In addition, the FEV₁/FVC ratio was similar between the FAO and non-FAO groups from the ages of 6 to 8 years old; however, the FEV₁/FVC ratio was lower in the FAO group than in the non-FAO group for patients between the ages of 10 to 18 years (*P* < .05; Figure 3). Compared with the non-FAO group, the BD response rate of the FAO group was higher at baseline but became lower at the 4-year follow-up (*P* < .05; Table 2).

The univariate logistic regression analysis observed that FAO was associated with the following variables: age, BMI,

hospitalizations for asthma, BD response, frequent exacerbations, length of exacerbations, and asthma severity (Figure 4). The multiple logistic regression analysis revealed that only the frequent exacerbations and asthma severity (steps 4-5 category) were independently associated with FAO (RRs of 4.0 and 3.5, respectively; *P* < .05; Table 3).

4 | DISCUSSION

This study showed that the incidence of FAO in children and adolescents was 9.5%. We also showed that the incidence of FAO was higher in children older than 10 years of age. Finally, we demonstrated that frequent exacerbations and asthma severity categorized as steps 4 to 5 were considered risk factors for FAO development in children and adolescents with asthma.

FIGURE 2 Incidence of FAO between asthma severity groups. A higher incidence of FAO was observed in the patients with asthma severity in the steps 4 to 5 category than in patients with asthma severity in the steps 1 to 2 and 3 categories (* $P < .001$). The χ^2 test was used to compare the asthma severity groups. FAO, fixed airflow obstruction

To the best of our knowledge, this study is the first to evaluate the incidence of FAO in children and adolescents with asthma. Previous studies evaluated the abnormal patterns of lung function from childhood into adulthood, but they did not evaluate FAO.⁸⁻¹⁵ Some studies have demonstrated that patients with asthma present patterns of reduced lung function during childhood,^{10,12,13,15} while others have shown that reduced lung function occurs only during adulthood.^{8,9,11} We consider that our study adds to the literature because all patients had normal lung function at baseline, developed FAO during the follow-up and had clinical treatment established

FIGURE 3 Mean FEV₁/FVC ratio according to age in years. After 10 years of age, the FEV₁/FVC ratio was lower in the FAO group than in the non-FAO group (* $P < .05$). The Student *t* test was used to compare age in the FAO and non-FAO groups. FAO, fixed airflow obstruction, FEV₁, forced expiratory volume in first second, FVC, forced vital capacity

according to the GINA guidelines.¹ Our results demonstrated that the incidence of FAO was higher in children and adolescents with severe asthma than in those with mild to moderate disease. FAO was defined using the LLN criteria in our study and recent recommendations advocate using the LLN rather than using a fixed-value FEV₁/FVC ratio criterion because the LLN avoids misclassification.^{6,29}

In our cohort, the variables older age, increased BMI, hospitalizations for asthma, BD response, frequent exacerbations, length of exacerbations, and asthma severity were independently associated with FAO. However, after the multiple logistic regression analysis, only the frequent

TABLE 2 Spirometry data at baseline and during follow-up between the FAO and non-FAO groups

	All n = 358	FAO n = 34	non-FAO n = 324	P value
FVC% predict, pre-BD				
Baseline	96 ± 12	97.8 ± 11.3	95 ± 12.4	.24
Follow-up	96.8 ± 11.9	98 ± 13.1	95.1 ± 10.4	.12
FVC% predict, post-BD				
Baseline	97.8 ± 12	99 ± 11	97 ± 12.4	.36
Follow-up	100.9 ± 11	102 ± 15	100.4 ± 11	.43
FEV ₁ % predict, pre-BD				
Baseline	95.3 ± 15	94.4 ± 10	96 ± 14.2	.52
Follow-up	91.8 ± 14.5	78.5 ± 8.8*	97.2 ± 12.1	<.001
FEV ₁ % predict, post-BD				
Baseline	99.2 ± 13.4	98.4 ± 14	100.4 ± 11.3	.33
Follow-up	94.1 ± 12.2	87.1 ± 13.1*	98.4 ± 10	<.001
FEV ₁ /FVC ratio, post-BD				
Baseline	0.86 ± 0.06	0.85 ± 0.06	0.86 ± 0.06	.35
Follow-up	0.83 ± 0.09	0.73 ± 0.08*	0.87 ± 0.05	<.001
BD response, change in FEV ₁ %				
Baseline	18.5 ± 15	29.7 ± 16.6	15 ± 12.3	<.001
Follow-up	13.2 ± 7.4	10 ± 6.5*	14 ± 7.9	<.001

Note: Data are presented as mean and standard deviation. The Student *t* test was used to compare baseline versus follow-up in the FAO and non-FAO groups. All subjects were followed during a 4-y follow-up. The BD response was considered a post-BD increase in FEV₁ of >12% predicted from the pre-BD value.

Abbreviations: BD, bronchodilator; FAO, fixed airflow obstruction; Δ FEV₁, variation of forced expiratory volume in the first second; FEV₁/FVC, forced expiratory volume in the first second/forced vital capacity.

* $P < .05$ when comparing baseline versus follow-up.

FIGURE 4 Solid and dashed arrows present the main risk factors and variables that could be associated with FAO, respectively. Multiple logistic regression analysis was used to evaluate risk factors for FAO. BD, bronchodilator; BMI, body mass index; FAO, fixed airflow obstruction

exacerbations and asthma severity categorized as steps 4 to 5 remained risk factors for FAO. It is difficult to compare our results with those of previous studies in the literature because no previous study has evaluated the risk factors for FAO in children and adolescents. There is evidence that BMI,^{11,15,30} age,^{11,13} second-hand smoke,^{11,15} respiratory tract infection,¹⁵ prematurity,¹⁵ and corticosteroid dose³⁰ are the main risk factors for patterns of reduced lung function in children and adolescents with asthma. Our results are supported by previous studies with adults suggesting that frequent asthma exacerbation and severe asthma are risk factors for FAO in adults.^{31,32} Thus, the risk factors for FAO in children and adolescents seem to be quite similar to those observed in adults. As a consequence, these results suggest that children and adolescents with frequent exacerbations and asthma severity categorized as steps 4 to 5 have increased the risk of developing FAO in both childhood and adulthood.

Sears et al⁸ and McGeachie et al¹¹ observed that children presenting with abnormal lung function after the age of 10 years had lower lung function in adulthood. In our study, the onset of FAO started at 10 years of age. The patients in the FAO and non-FAO groups had similar ages at onset of the start of treatment; however, the FAO group was older than the non-FAO group. The FAO group may have been older because they experienced a higher frequency of exacerbations over a longer period (Table 1).

Recent studies reported that patients with asthma during childhood who present greater airway variability between medical visits (either FEV₁ or FVC) are likely to present impaired lung function over their lifespan.³³ In the present study, we observed that children and adolescents with asthma who presented better BD responses at baseline had a higher likelihood of developing FAO. A possible explanation for our results is based on the fact that patients with higher FEV₁ responses post-BD also present greater airway hyperresponsiveness and inflammation.³⁴ As a consequence, persistent inflammation could lead to airway remodeling and airflow limitation, thereby reducing the airway-parenchymal interdependence.³⁵ However, we did not evaluate airway inflammation, and this

TABLE 3 Multiple logistic regression analysis for risk factors for FAO development in children and adolescents with asthma

	Risk relative	95% CI	P value
Frequent exacerbations	4.0	1.3-11.7	.002
Asthma severity categorized as steps 4-5	3.5	1.6-7.6	<.001

Note: Multiple logistic regression analysis shows the main explanatory variables to FAO development. Frequent exacerbations were considered ≥ 3 episodes of asthma requiring OC treatment in the previous 12 mo. Participants requiring a moderate or high daily dose of an ICS associated with LABA were considered to have asthma severity in the steps 4-5 category.

Abbreviations: CI, confidence interval; FAO, fixed airflow obstruction; ICS, inhaled corticosteroid; LABA, long-acting β_2 -agonist; OC, oral corticosteroid.

hypothesis remains to be investigated in the near future. Another hypothesis for the cause of the fixed airflow obstruction observed in the FAO group is dysanaptic lung growth. Dysanaptic lung growth is defined as an incongruence between the growth of the lung parenchyma and the caliber of the airway, as observed by an abnormal FEV₁/FVC ratio, with the FEV₁ in the normal range.^{36,37} Interestingly, the FAO group presented FEV₁ values of approximately 80% of the predicted values at the 4-year follow-up.

Our study has limitations. First, we evaluated FAO until adolescence, and we cannot establish that patients who did not develop FAO during our study will not develop it in adulthood; however, this was not our aim. Second, the incidence of FAO in our patients was 9.5%, which limited the number of variables that could be included in the multiple logistic regression. As a consequence, other variables could have relevance in a larger sample size; however, our sample size is larger than that used in most studies performed with adults.^{32,33,38,39} Third, the asthma history variable was obtained from the patients' parents and may depend on their memories; however, this was the only variable that depended on the parents' memories. Fourth, we did not evaluate second-hand smoke inhalation; however, in our clinical practice, caregivers are always reminded to not smoke in homes where children and adolescents with asthma live.

5 | CONCLUSION

Children and adolescents with asthma who present with frequent exacerbations and receive higher doses of inhaled corticosteroids to maintain asthma control have a greater risk of developing FAO. Measures to prevent frequent exacerbations could help to avoid reduced lung functional capacity. More studies of FAO in childhood will help to increase our knowledge of airway changes.

ACKNOWLEDGMENTS

The authors would like to acknowledge the collaboration with the Darcy Vargas Hospital during participant's enrollment. In addition,

we thank the children and their parents who agreed to participate in this study.

CONFLICT OF INTERESTS

The protocol was submitted and approved by the Hospital Research Ethics Committee, and all family caregivers gave written signed consent. All authors state that no companies have provided grants, gifts, equipment, or drugs to this study or any participants. In addition, no tobacco companies have funded any part of this manuscript. Any unexpected adverse effects or changes in protocols have been disclosed. The principal author contributed to the entire manuscript preparation and takes full responsibility for the integrity and accuracy of the data.

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How to cite this article: Sousa AW, Barros Cabral AL, Arruda Martins M, Carvalho CRF. Risk factors for fixed airflow obstruction in children and adolescents with asthma: 4-Year follow-up. *Pediatric Pulmonology*. 2020;1-8. <https://doi.org/10.1002/ppul.24625>

6.3 Artigo: Avaliação física na obstrução fixa das vias aéreas

ORIGINAL ARTICLE: ASTHMA

Physical fitness and quality of life in adolescents with asthma and fixed airflow obstruction

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Funding information

Fundação de Amparo à Pesquisa do Estado de São Paulo, Grant/Award Number: 2016/05968-1; Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Grant/Award Number: 312.279/2018

Abstract

Asthma is a disease characterized by reversible bronchoconstriction, but some subjects develop fixed airflow obstruction (FAO). Subjects with FAO present more asthma symptoms and may have increased sedentary behavior; however, the effect of FAO on aerobic fitness and physical activity levels (PAL) remains poorly understood.

Aim: To compare adolescents with asthma and FAO and adolescents with asthma without FAO in terms of aerobic fitness, PAL, muscle strength, and health-related quality of life (HRQoL).

Methods: This cross-sectional study included adolescents with asthma, both sexes, and aged 12–18 years. They were divided into two groups: FAO and non-FAO groups. The adolescents were diagnosed with asthma according to the Global Initiative for Asthma guidelines and underwent optimal pharmacological treatment for at least 12 months. FAO was diagnosed when the forced expiratory volume in the first second/forced vital capacity ratio was below the lower limit of the normal range after optimal treatment. Aerobic fitness, PAL, peripheral and respiratory muscle strength, and HRQoL were evaluated.

Results: No significant differences were observed between FAO and non-FAO groups regarding the peak oxygen uptake (34.6 ± 8.5 vs. 36.0 ± 8.4 mL O₂/min/kg), sedentary time (578 ± 126 vs. 563 ± 90 min/day), upper limb muscle strength (29.1 ± 5.9 vs. 28.1 ± 5.7 kilograms of force [kgf]), lower limb muscle strength (42.8 ± 8.6 vs. 47.6 ± 9.6 kgf), or HRQoL (5.1 ± 1.3 vs. 4.7 ± 1.4 score; $p > .05$). However, the FAO group exhibited a higher maximal expiratory pressure than the non-FAO group (111.5 ± 15.5 vs. 101.5 ± 15.0 cmH₂O, respectively).

Conclusion: Our results suggest that FAO does not impair aerobic fitness, PAL, peripheral muscle strength, or HRQoL in adolescents with asthma. Furthermore, adolescents with asthma were physically deconditioned.

KEYWORDS

accelerometer, irreversible, muscle strength, physical activity, steps

1 | INTRODUCTION

Asthma is a chronic disease characterized by airway inflammation and is diagnosed if a subject has a history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, coughing, and variable airflow obstruction.¹ Airflow obstruction can often be reversed either spontaneously or with pharmacological treatment.¹ However, approximately 10% of children and adolescents with asthma in a previous study exhibited an expiratory airflow limitation that was not completely reversible, despite optimal treatment being provided²; this condition is known as fixed airflow obstruction (FAO).³

FAO is diagnosed when a subject's ratio of the forced expiratory volume in the first second (FEV₁) to the forced vital capacity (FVC) (FEV₁/FVC) is below the lower limit of the normal range (LLN) after optimal treatment.³ The development of FAO has been explained by a type of pathological airway remodeling that leads to structural changes in the airway and airflow restrictions.⁴ The risk factors for FAO are multifactorial and differ between adults and children.^{2,5} The main risk factors for FAO in adults include a subject's sex, smoking habits, the presence of rhinitis, atopy, and eosinophil inflammation, and the amount of fractional exhaled nitric oxide.⁵ In children and adolescents, the risk factors are related to asthma severity and the frequency of exacerbations.²

Previous studies have reported that subjects with FAO exhibit higher asthma hospitalization rates and more severe symptoms such as dyspnea, wheezing, and chest tightness than do their non-FAO peers.^{2,4} The fear of feeling asthma symptoms could inhibit many subjects from taking part in regular physical activity due to exercise-induced bronchoconstriction.⁶ The current guidelines encourage subjects with asthma to engage in regular physical activity.¹ An increase in the subject physical activity level (PAL) improves the aerobic fitness and health-related quality of life (HRQoL) and reduces the need for inhaled corticosteroids (ICS), asthma exacerbations, and dyspnea symptoms.⁷ In addition, adolescents with asthma who remain physically active exhibit a slower annual decline in FEV₁ and FEV₁/FVC ratio values than do those who are physically inactive.⁸ Although the benefits of regular physical activity are well known, adults with asthma and FAO are physically inactive and exhibit low levels of aerobic fitness^{8,9}; however, the effects of FAO in adolescents with asthma remain poorly understood.

In the present study, we hypothesized that adolescents with asthma and FAO have lower levels of aerobic fitness, PAL, muscle strength, and HRQoL than do their peers with asthma but without FAO. Our study aimed to compare adolescents with FAO and their non-FAO peers in terms of aerobic fitness, PAL, muscle strength, and HRQoL.

2 | METHODS

2.1 | Subjects

This cross-sectional study was conducted in adolescent outpatients with asthma who were recruited from a tertiary university hospital. Asthma was diagnosed in accordance with the Global Initiative for

Asthma (GINA) guidelines.¹ The inclusion criteria were having undergone medical treatment for at least 12 months according to GINA guidelines,¹ being between 12 and 18 years old, steps from 3 to 5 of the asthma severity, and having clinically stable disease (no hospitalizations, emergency care visits, or medication changes in the last 30 days). There were no restrictions regarding sex. The exclusion criteria were cardiovascular, neuromuscular, neurological, or any other pulmonary diseases. The adolescents were divided into two groups: asthma with FAO (FAO group) and asthma without FAO (non-FAO group) groups. The non-FAO group included outpatients under optimal medical treatment in the same hospital who were recruited using the frequency matching method¹⁰ based on sex, age, and body mass index (BMI) to avoid bias in the comparisons. Adolescents were included in the non-FAO group in small groups of five. Then, every time that five adolescents were included in the FAO group, the subsequent five subjects were included in the non-FAO group until the total sample size was reached.

The Hospital Research Ethics Committee approved the study, and written informed consent was obtained from the adolescents' caregivers. The costs of transport for all adolescents and their caregivers were covered by the researchers to avoid dropouts. No financial compensation was offered to participate in the study.

2.2 | Study design

2.2.1 | Protocol

The adolescents were recruited during a regular medical visit, and they were assessed over 2 days with a 1-week interval. On the first day, the adolescents performed muscle strength assessment tests, completed the HRQoL questionnaire, and received a triaxial accelerometer to wear on their waist for 7 days. On the second visit, the adolescents returned the accelerometer and performed a maximal cardiopulmonary exercise test (CPET). This study was conducted between August 2018 and March 2019. Blinded assessors to the group allocation performed all assessments.

2.3 | Assessment

2.3.1 | Fixed airflow obstruction

FAO was defined as the ratio of the FEV₁/FVC persistently below the LLN, according to reference equations, even after the use of a postbronchodilator (BD).³ For adolescents with FEV₁/FVC ratios persistently lower than the LLN on two consecutive visits, oral corticosteroids (OC) were prescribed for 7 successive days, in addition to the ICS and long-acting beta2-agonist. The OC dose was 1 mg/kg of body weight for adolescents up to 40 kg; for those over 40 kg, a maximum dose of 40 mg/day was prescribed.¹ After 7 days of treatment, the adolescents returned to the hospital and underwent a

new spirometry test. The presence of FAO was noted if the FEV₁/FVC ratio remained lower than that of LLN.³

2.3.2 | Lung function

The lung function test was evaluated using a spirometer (Koko Digi-Doser) coupled with a microcomputer. The technical procedure, eligibility criteria, and reproducibility were established in accordance with the recommendations of the American Thorax Society and European Respiratory Society.¹¹ The following variables were assessed: FEV₁, FVC, and the FEV₁/FVC ratio. Spirometry was performed before and after 400 µg of salbutamol inhaled at an interval of 10–15 min to evaluate the BD response.¹¹ A positive BD response was considered if a post-BD increase in FEV₁ of more than 12% was predicted from the pre-BD value.¹¹ Values were compared with the values predicted based on data from a Brazilian population, and the LLN was evaluated by a program provided by the Global Lung Initiative.¹¹

2.3.3 | Asthma control

The Asthma Control Test (ACT), validated for Brazilian Portuguese use, was used to assess the level of asthma control.¹² The ACT has five questions regarding activity limitation, shortness of breath, and nighttime symptoms experienced over the last 4 weeks. Each question has five response options ranging from 1 (worst) to 5 (best). The ACT scores range from 0 (totally uncontrolled asthma) to 25 (totally controlled asthma), and scores ≥20 indicate controlled asthma.¹²

2.3.4 | Anthropometric data and BMI

BMI was calculated by dividing the subjects' weight in kilograms by their height in square meters (kg/m²).¹³ The weight status categories were underweight (<5th), normal weight (5th to <85th), overweight (85th to <95th), and obese (≥95th).

Frequent exacerbations

An exacerbation was defined as an acute episode of increased symptoms and deterioration in lung function requiring OC treatment.¹ Patients who had ≥3 episodes of asthma exacerbation for 12 months at any point in their life were considered to have frequent exacerbations.²

Allergies

The total immunoglobulin E (IgE) levels were measured using the immunoenzymatic assay method. The specific IgE test was conducted using the Phadiatop method (Phadia 100; Thermo Fisher Scientific, Phadia AB). The specific IgE test was considered positive if it was ≥0.35 kUA.¹⁴ The number of allergens refers to allergens that can trigger allergies, such as pollen, dust mites, mold, animal hair, cockroach, or mouse epithelium.¹⁴

2.3.5 | Health-related quality of life

HRQoL was assessed using the Pediatric Asthma Quality of Life Questionnaire (PAQLQ), which includes three domains: activity limitations, symptoms, and emotional function.¹⁵ The PAQLQ consists of 23 items rated on a 7-point scale (from 1 to 7), and a higher score indicates a better quality of life.¹⁵

2.3.6 | Peripheral muscle strength

For upper and lower limb muscle strength, handgrip strength was measured using a hand dynamometer (Jamar hydraulic; Lafayette), and quadriceps strength was measured using a load cell (EMG System). In both assessments, the dominant limbs were used, and all adolescents were asked to sustain maximum force for 5 s with maximal verbal encouragement during the test. A minimum of three trials and a maximum of five trials were performed for each test. The interval between measurements was approximately 1 min, and the best value from three acceptable trials presenting a variation of less than 10% were considered. The isometric force is expressed in kilograms of force (kgf) and the percentage of the predicted values. The predicted values were obtained from a Brazilian population and stratified by sex, age, and weight.¹⁶

2.3.7 | Respiratory muscle strength

Respiratory muscle strength was assessed by measuring maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP). The test was performed using a digital manovacuometer (MVD 300-U; Globalmed). The device was connected to a tube coupled to a sterilized filter that was attached to a mouthpiece. The assessments were performed in a seated position while the subject wore a nose clip. The MIP was assessed after maximal expiration near the residual volume, while MEP was assessed after maximal inspiration near the total lung capacity.¹⁷ Both measurements were performed with maximum effort and sustained for at least 1 s. The number of repetitions, interval time, and best value from the acceptable trials were used for analysis, as in the assessment of peripheral muscle strength. The respiratory muscle strength values were expressed in cmH₂O and the percentage of predicted values. The predicted values were obtained from a Brazilian population and stratified by sex, age, height, and weight.¹⁸

2.3.8 | Physical activity level

PAL was objectively quantified using a movement sensor (ActiGraph GT3X; ActiGraph). All units were initialized via a computer interface, and data were collected in 15-s epochs in all three dimensions using specific software (ActiLife 6.9.5, firmware version). Each adolescent was instructed to wear the movement sensor on the hip (non-dominant side) using an elastic belt for 7 consecutive days. The data are presented as the average number of steps per day and the time

spent performing moderate-to-vigorous physical activity (MVPA), performing light-intensity physical activity, and sitting.¹⁹ Adolescents were considered successfully monitored when they used the accelerometer for at least 4 days for more than 10 h per day.

2.3.9 | Cardiopulmonary exercise test

The CPET was performed using the Vyntus CPX (Carefusion) linked to a gas analysis system (CardiO₂ System; Medical Graphics Corporation). The adolescents performed a ramp-symptom-limited CPET consisting of 2 min of rest, 3 min of warm-up (unloaded pedaling), and an incremental work period (15 W/min for height <150 cm and 20 W/min for height ≥150 cm).⁷ During the test, the adolescents were instructed to continue pedaling at 60 rpm. The test was set to last from 8 to 12 min until 90% of the maximal heart rate (HR) predicted was reached, and 1.10 of the respiratory exchange rate (RER) was considered available.⁷ Oxygen saturation (SpO₂) was measured via pulse oximetry (Onyx, model 9500; Nonin), and electrocardiography signals (Welch Allyn CardioPerfect, Inc) were monitored continuously during the tests. The following variables were recorded: power, peak oxygen uptake (VO_{2peak}), minute ventilation (VE), carbon dioxide production (VCO₂), RER, and HR. In addition, blood pressure, Borg score for leg discomfort, and severity of dyspnea were measured at rest and every 2 min during the test until the end of the test.²⁰ Males and females were considered to have good aerobic fitness when they reached VO_{2peak} ≥43.4 and ≥35.6 ml/kg/min, respectively. If these thresholds were not met, they were considered to have low aerobic fitness.²¹ The tests were performed in accordance with the recommendations of the American Thoracic Society. The predicted CPET values were calculated for the Brazilian population.²²

2.4 | Statistical analysis

A sample size of 20 adolescents per group was estimated to be needed to detect a difference of 6 ml/kg/min with a standard deviation of 6 ml/kg/min in the VO_{2peak}.²³ The final sample size was 22 adolescents per group, assuming a loss of up to 10%. The sample size was calculated to provide 80% power and an alpha level of 0.05. The normality of the data was evaluated using the Kolmogorov–Smirnov test. The between-group comparisons of the categorical variables and the analysis of the differences in the proportions of adolescents across groups were performed using the χ^2 test or Fisher's test. For the between-group comparisons of the continuous variables, the *t* test or Mann–Whitney test was used. The data were analyzed using the Statistical Package for Social Science (SPSS) software, version 22.0.

3 | RESULTS

3.1 | Adolescents' characteristics

A total of 44 adolescents were screened; two terminated their participation in the study, and one experienced exacerbated symptoms before the 2nd visit (Figure 1). Most of the adolescents were male and had a normal weight, controlled asthma (ACT ≥20), early onset asthma, and atopic conditions (Table 1). The adolescents in the FAO group reported more previous asthma hospitalizations, more cases of early onset asthma, and more cases of atopic conditions. Besides, they presented poorer lung function (FEV₁ and FEV₁/FVC ratio) and a poorer BD response than the non-FAO group (*p* < .05; Table 1). On the other hand, no significant differences were observed between FAO and non-FAO groups in terms of sex, BMI, ICS dose, ACT score,

FIGURE 1 STROBE diagram of the study

TABLE 1 Anthropometric characteristics of asthma and spirometric data in the FAO and non-FAO groups

	All n = 41	FAO n = 20	non-FAO n = 21	p Value
Anthropometric data				
Male, n (%)	25 (61)	12 (60)	13 (62)	.90
Age, years-old	15.6 ± 1.8	15.8 ± 1.9	15.5 ± 1.8	.63
BMI percentile	62.0 ± 26.9	62.5 ± 29.7	61.6 ± 24.7	.91
BMI classification, n (%)				
Normal weight	30 (73)	14 (70)	16 (76)	.92
Overweight/obese	11 (27)	6 (30)	5 (24)	
Asthma-related variables				
Asthma severity, n (%)				
Step 3	16 (39)	8 (40)	8 (38)	
Steps 4–5	25 (61)	12 (60)	13 (62)	.88
Budesonide equivalent dose, µg	634 ± 199	660 ± 195	609 ± 204	.42
ACT score	22.9 ± 1.9	22.7 ± 1.8	23.1 ± 2.0	.51
Asthma hospitalization, n (%)[*]				
Yes	26 (63)	16 (80)	10 (48)	
No	15 (37)	4 (20)	11 (52)	.05
Frequent exacerbation, n (%)				
Yes	30 (73)	16 (80)	13 (62)	.30
No	11 (27)	4 (20)	8 (38)	
Subjects who required OC in the past 12 months, n (%)				
Yes	8 (19.5)	4 (20)	4 (19)	.75
No	33 (80.5)	16 (80)	17 (81)	
Onset asthma, n (%)[*]				
Early, <2 years old	25 (61)	15 (75)	9 (43)	.04
Late, ≥2 years old	16 (39)	5 (25)	12 (57)	
Allergic markers				
Blood eosinophils, %	10.0 ± 7.1	10.7 ± 8.6	9.6 ± 6.4	.73
IgE total, U/ml [*]	1621 ± 1387	2528 ± 1570	1077 ± 979	<.01
Number of allergens [*]	2.4 ± 0.8	2.8 ± 0.8	2.1 ± 0.8	<.01
Lung function				
FVC post-BD, (L),	3.89 ± 0.76	4.05 ± 0.91	3.75 ± 0.57	.23
% of predicted,	101.6 ± 14.6	103 ± 17.5	100.3 ± 11.6	.57
z-score	−0.03 ± 1.2	0.22 ± 1.28	−0.23 ± 1.1	.23
FEV ₁ post-BD, (L) [*] ,	3.05 ± 0.50	2.88 ± 0.53	3.21 ± 0.46	.04
% of predicted [*] ,	92.7 ± 14.5	86.2 ± 15.6	98.6 ± 10.7	<.01
z-score [*]	−0.79 ± 1.1	−1.4 ± 0.93	−0.34 ± 0.99	<.01
FEV ₁ /FVC ratio, post-BD [*] ,	0.79 ± 0.08	0.72 ± 0.06	0.85 ± 0.04	<.01
z-score [*]	−1.08 ± 1.19	−2.21 ± 0.53	−0.23 ± 0.75	<.01
BD response, % FEV ₁ change [*]	10.6 ± 4.3	8.2 ± 4.0	12.4 ± 4.5	<.01

Note: Data are presented as mean ± SD or number (%). BMI was calculated by dividing weight in kilograms by heights in square meter.¹³ Budesonide equivalent dose was calculated according to Fanelli et al.⁷ Asthma hospitalization refers to any hospitalization in a lifetime. Frequent exacerbation was considered when subjects had ≥3 episodes of asthma exacerbation either during the last 12 months or at any point in their lifetime.² Early-onset asthma was defined as asthma symptoms beginning before the second birthday.² The number of allergens refer to those that could trigger allergies such as pollen, dust mites, mold, animal hair, cockroach, or mouse epithelium. The z-score refers to the raw score from the mean, and it is calculated using the patient value, the sample means, and sample standard deviation. FAO group presented more hospitalization, early-onset asthma, higher IgE total, and the number of allergens than the non-FAO group. FEV₁ percentage of predict, FEV₁/FVC ratio, and BD response were lower in FAO than the non-FAO group ($p < .05$). The bold values represent difference significant.

Abbreviations: n, number; ACT, asthma control test; BD, bronchodilator; BMI, body mass index; IgE, immunoglobulin E; FAO, fixed airflow obstruction; FEV₁, forced expiratory volume in the first second; FVC, forced vital capacity; µg, micrograms; L, litre; OC, oral corticosteroids; U/ml, units per millilitre.

* $p < .05$ Comparing the FAO with the non-FAO groups. The χ^2 and the Student t test were used to compare categorical and continuous variables, respectively.

frequent exacerbation, OC required in the past 12 months, blood eosinophils, and FVC % of the predicted value ($p > .05$; Table 1).

3.2 | Aerobic fitness

Most adolescents in both the FAO and non-FAO groups had low aerobic fitness, with proportions of 85% and 76%, respectively ($p > .05$). No significant differences were observed between groups in the VO_2 peak, minute ventilation, and oxygen pulse recorded during the CPET ($p > .05$, Table 2). During maximal exercise, ventilation was not considered a limiting factor; however, cardiac function was near the maximal limit (Table 2). Peripheral muscle fatigue was more severe than was dyspnea perception ($p < .05$; Table 2), and all adolescents requested to stop the CPET due to lower limb fatigue.

3.3 | Physical activity levels

The FAO and non-FAO groups spent most of their time performing sedentary behavior (72.9% and 73.4%, respectively; $p > .05$). No significant differences in the number of steps per day, sedentary time, or time performing light or MVPA were observed between the FAO and non-FAO groups ($p > .05$; Table 3).

3.4 | Peripheral and respiratory muscle strength

The inspiratory, handgrip, and quadriceps femoral muscle strength values were similar between the FAO and non-FAO groups ($p > .05$; Table 3). On the other hand, the expiratory muscle strength values were higher in the FAO group than in the non-FAO group ($p < .05$; Table 3).

3.5 | Health-related quality of life

The FAO and non-FAO groups presented no significant differences in the total PAQLQ score (respectively, 5.1 ± 1.3 vs. 4.7 ± 1.4 score; $p > .05$) or in the scores for the three domains: physical activity (respectively, 5.2 ± 1.1 vs. 4.8 ± 1.2 score; $p > .05$); symptoms (respectively, 4.9 ± 1.3 vs. 4.5 ± 1.3 score; $p > .05$); emotions (respectively, 5.1 ± 1.5 vs. 4.7 ± 1.6 score; $p > .05$).

4 | DISCUSSION

Our results showed that adolescents with FAO and non-FAO adolescents presented similar aerobic fitness, PAL, peripheral muscle strength, and HRQoL results. However, the adolescents in the FAO group presented higher values of expiratory muscle strength than did the non-FAO group. This study also showed that most adolescents with asthma

TABLE 2 Aerobic fitness in the FAO and non-FAO groups

	All <i>n</i> = 41	FAO <i>n</i> = 20	non-FAO <i>n</i> = 21	<i>p</i> Value
Anaerobic threshold				
Power, W	110 ± 31	106 ± 35	116 ± 27	.27
VO_2 , ml/min/kg,	26.5 ± 7.9	26.3 ± 7.7	26.6 ± 8.3	.91
% of predicted	49.0 ± 12.7	49.1 ± 12.5	48.9 ± 12.8	.92
Minute ventilation, L/min	45.3 ± 11.0	47.3 ± 10.8	43.3 ± 11.0	.25
Aerobic threshold				
Power, W	156 ± 35	150 ± 41	163 ± 27	.20
VO_2 , ml/min/kg,	35.4 ± 8.4	34.6 ± 8.5	36.0 ± 8.4	.61
% of predicted	68.8 ± 16.0	67.6 ± 16.1	70.1 ± 15.9	.61
Minute ventilation, L/min	78.9 ± 14.6	77.3 ± 16.6	80.3 ± 12.8	.53
Ventilatory reserve, % of predicted	27.6 ± 15.0	26.4 ± 13.3	28.7 ± 16.7	.62
Cardiac reserve, % of predicted	6.3 ± 3.0	6.8 ± 2.9	5.9 ± 3.1	.67
Heart rate, bpm	186 ± 9.4	187 ± 8.3	186 ± 10.3	.73
VO_2 /HR, ml/bpm	7.9 ± 1.9	8.4 ± 2.4	7.5 ± 1.3	.14
$\Delta VO_2/\Delta W$, ml/min/W	17.1 ± 3.9	16.7 ± 3.7	17.5 ± 4.1	.51
Fatigue perception (Borg score) [†]	17.3 ± 2.4	17.3 ± 2.3	17.4 ± 2.5	.86
Dyspnoea perception (Borg score) [†]	16.1 ± 2.9	16.4 ± 2.3	15.8 ± 3.5	.56

Note: Aerobic fitness are presented as mean ± SD. Fatigue and dyspnoea perception score were evaluated by Borg scale (Borg scale 6–20).²⁰ FAO and non-FAO groups presented similarity on the aerobic fitness analysis (the Student *t* test; $p > .05$).

Abbreviations: bpm, beats per minutes; FAO, fixed airflow obstruction; L/min, liters per minutes; ml/min, millilitres per minutes; ml/min/kg: millilitres per minutes per kilogram; *n*, number; W, watts; VO_2 , oxygen consumption; VO_2 /HR, oxygen pulse; $\Delta VO_2/\Delta W$, peripheral muscle efficiency.

[†] $p < .05$ Compared fatigue and dyspnoea perception in the same group.

	All n = 41	FAO n = 20	non-FAO n = 21	p Value
Data of accelerometer				
Sedentary behaviour, min/day	570 ± 108	578 ± 126	563 ± 90	.56
Light, min/day	90.0 ± 21.6	94.2 ± 29.4	85.8 ± 12	.23
Moderate-to-Vigorous, min/day	24.6 ± 13.1	23.6 ± 15.2	25.6 ± 10.9	.63
Total steps per day	7248 ± 2826	7508 ± 2926	7001 ± 2780	.58
Respiratory muscle strength				
MIP, cmH ₂ O,	-105.4 ± 11.0	-103.0 ± 8.9	-105.7 ± 12.9	.56
% of predicted	90.1 ± 17.5	88.4 ± 16.4	91.7 ± 18.3	.54
MEP, cmH ₂ O,*	106.1 ± 15.0	111.5 ± 15.5 [†]	101.5 ± 15.0	.04
% of predicted*	102.5 ± 14.4	108.1 ± 14.8	97.2 ± 14.1	.02
Peripheral muscle strength				
Upper limb, kgf,	28.8 ± 5.7	29.1 ± 5.9	28.1 ± 5.7	.58
% of predicted	52.6 ± 7.4	53.3 ± 7.3	51.7 ± 7.4	.49
Lower limb, kgf,	45.4 ± 9.1	42.8 ± 8.6	47.6 ± 9.6	.11
% of predicted	49.3 ± 10.8	46.4 ± 9.9	51.6 ± 11.5	.13

Note: Data are presented as mean ± SD. Physical activity level was measured by accelerometer and quantified, according to Freedson et al.¹⁹

Respiratory muscle strength was measured by a digital manovacuometer. Upper and lower limbs were evaluated by handgrip and quadriceps femoral strength, respectively.

Abbreviations: cmH₂O, centimetre of water; FAO, fixed airflow obstruction; kgf, kilogram-force; MEP, maximal expiratory pressure; min/d, minutes per day; MIP, maximal inspiratory pressure; n, number.

**p* < .05 Comparing the FAO and the non-FAO groups (the Student *t* test).

TABLE 3 Physical activity level and muscle strength measured by accelerometer in the FAO and non-FAO groups

are physically deconditioned and sedentary, regardless of whether the condition was clinically controlled, and FAO was present.

Aerobic fitness and PAL in children and adolescents with asthma have been studied over the last two decades,^{24–26} and the association between PAL and lung function remains poorly understood.²⁷ Lopenen et al.⁸ showed that a low PAL was associated with a faster decline in lung function in adults with asthma. However, no studies have evaluated the association between PAL and the decline in lung function in children and adolescents with asthma. Contrary to our hypothesis, the present study showed that the FAO and non-FAO adolescents have similar PAL. Two hypotheses can explain our findings. First, both groups had controlled asthma, and this hypothesis is supported by previous studies showing that subjects with controlled asthma experience fewer asthma symptoms and therefore have a higher PAL than subjects with uncontrolled asthma.²⁸ Second, both groups exhibited a long period of sedentary behavior and a very short period of MVPA.

In our study, most adolescents in the FAO and non-FAO groups presented reduced levels of aerobic fitness, as evaluated by the CPET. These results corroborate previous studies showing that children and adolescents with asthma present reduced levels of aerobic fitness.^{7,22,23} The low aerobic fitness level observed in both groups in our study may be explained by the reduced MVPA levels. All adolescents presented higher scores of fatigue perception and cardiac limitation than dyspnea perception and ventilatory limitation during the maximal exercise performance. These results suggest that reduced aerobic fitness could cause interruption during maximal exercise rather than either asthma or FAO. Interestingly, the opposite was

observed in adolescents with asthma, presenting an excellent aerobic fitness, or being subjected to a physical training program.²⁹

Children and adolescents with asthma and nonasthmatic peers have been shown to have similar levels of respiratory muscle strength.³⁰ On the other hand, children and adolescents with severe asthma have reduced MIP compared to those with nonsevere asthma.³¹ This difference probably occurs because airway obstruction leads to static hyperinflation and places the respiratory muscle at a mechanical disadvantage.³² Interestingly, we observed that adolescents with FAO exhibit a higher MEP than do non-FAO adolescents. This finding can be explained by the fact that the lower the airway caliber, the greater the respiratory requirement for exhaling air from the lungs.³²

Several studies have evaluated upper and lower peripheral muscle strength in children and adolescents with asthma,^{23,33,34} and most of them did not observe differences between subjects with asthma and their nonasthmatic peers.^{23,33} Our results showed that the upper and lower limb muscle strength values were similar between the FAO and non-FAO groups. In contrast, Lattorre-Romám et al.³⁴ demonstrated different handgrip strength results in subjects with asthma. The authors reported that subjects with a lower FEV₁ also had poorer handgrip strength.³⁴ The discrepancy between the results presented by Lattorre-Romám et al.³⁴ and our results may have occurred because Lattorre-Romám et al.³⁴ evaluated adolescents with asthma in steps 1–5, while we assessed adolescents with asthma in steps from 3 to 5 (mostly severe asthma). Interestingly, in our study, both groups exhibited reduced muscle strength in the upper and lower limbs (approximately 50% of predicted), suggesting that both the FAO and non-FAO groups have

muscle weakness. Muscle weakness might be explained by the fact that subjects with moderate-to-severe asthma are more sedentary and present a high number of exacerbations.³⁵ Our study showed that both groups presented a high percentage of frequent exacerbations at any point in their life. These exacerbations increased OC's consumption, reducing muscle strength, mainly in sedentary subjects.³⁶

The HRQoL scores were similar between the FAO and non-FAO groups in all the questionnaire domains (physical activity, emotions, and symptoms). Amaral et al.³⁷ evaluated HRQoL in adolescents with a lower or normal peak expiratory flow, and did not observe any significant differences between them. Our results are supported by those of previous studies demonstrating that adolescents with controlled and partially controlled asthma have a better HRQoL.^{38,39} In addition, a worse HRQoL in subjects with uncontrolled asthma is associated with fewer symptom-free days.⁴⁰ Taken together, these results suggest that HRQoL in adolescents is more strongly related to asthma control than airflow obstruction.

Our study has some limitations. First, the sample size was calculated based on the VO_{2peak} . The absence of differences between FAO and non-FAO groups in the secondary outcomes could result in small sample size and an inadequate statistical power (<0.8 or 80%). Unfortunately, the FAO incidence was lower, and we had to recruit many adolescents for the FAO group to achieve the calculated sample size. Second, we did not include a group of adolescents without asthma. However, the most recent systematic review demonstrated no physical fitness differences between adolescents with and without asthma.²⁶ Third, physical deconditioning could be a confounding factor between groups; however, most adolescents with asthma were considered physically deconditioned.²⁴ Last, adolescents were selected based on spirometric parameters. A complete pulmonary function test (PFT) would be required to evaluate air trapping; however, we do not regularly perform PFT in asthmatic subjects. On the other hand, the LLN assessed by spirometry has been reported to be a useful index for detecting FAO.³

5 | CONCLUSION

Adolescents with asthma and FAO and those without FAO have similar levels of aerobic fitness, physical activity, peripheral muscle strength, and quality of life. However, adolescents with FAO have greater expiratory muscle strength. The low exercise capacity and the presence of muscle weakness observed in both groups may have occurred due to the high level of sedentarism.

ACKNOWLEDGMENTS

The authors thank the adolescents who agreed to participate in this study and their parents. The study was supported by São Paulo Research Foundation (FAPESP), Grants: 2016/05968-1; Coordenação de Aperfeiçoamento de Pessoal de Nível Superior–Brasil (CAPES)–Finance Code 001; Conselho Nacional de Desenvolvimento Científico e Tecnológico, Grants: 312.279/2018.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTION

Andrey Wirgues Sousa: conceptualization, data curation, investigation, methodology, project administration, validation, visualization, writing—original draft. Anna Lucia Barros Cabral: conceptualization, investigation, project administration, supervision. Ronaldo Aparecido Silva: data curation, investigation, software. Alfredo José Fonseca: investigation, software. José Grindler: software, resources. Milton Arruda Martins: project administration, resources. Celso RF Carvalho: conceptualization, formal analysis, methodology, project administration, resources, supervision, validation, visualization, writing—original draft.

ETHICS STATEMENT

The protocol was submitted to and approved by the Hospital Research Ethics Committee, and the family caregivers provided written informed consent. All authors state that the patients did not receive grants, gifts, equipment, or medication to participate in the study. In addition, no tobacco companies have funded the study.

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How to cite this article: Sousa AW, Cabral ALB, Silva RA, et al. Physical fitness and quality of life in adolescents with asthma and fixed airflow obstruction. *Pediatric Pulmonology*. 2020;1-9. <https://doi.org/10.1002/ppul.25160>

7. Discussão

7.1 Principais achados

Nossos resultados mostraram 3 *clusters* em crianças e adolescentes com asma. Os *clusters* 1 e 2 mostram função pulmonar normal e o *cluster* 2 também mostra inflamação. O *cluster* 3 mostra função pulmonar alterada. Uma das alterações da função pulmonar foi a obstrução fixa das vias aéreas (FAO). A incidência da FAO nas crianças e adolescentes com asma foi de 9,5% e os fatores de risco para o desenvolvimento da FAO foram as exacerbações frequentes e a gravidade da asma. Além disso, os adolescentes com asma associado ao desenvolvimento da FAO apresentaram similaridade nas variáveis de avaliação física quando comparado com seus pares sem FAO; exceto pela força dos músculos expiratórios, onde os adolescentes com FAO apresentam mais força que os adolescentes sem FAO.

7.2 Estudo dos fenótipos

Os estudos que realizaram análise de *cluster* em crianças e adolescentes com asma encontraram diferentes números de *clusters* [LEE et al. 2017; JUST et al. 2014; HOWRYLAK et al. 2014; FITZPATRICK et al. 2011]. Por exemplo, Howrylak et al. (2014) relataram a existência de 5 *clusters*, enquanto Fitzpatrick et al. (2011), Just et al. (2014) e Lee et al. (2017) observaram 4 *clusters*. Já o nosso estudo encontrou 3 *clusters*. Apesar da diferença no número de *clusters* entre os estudos, alguns fenótipos são comuns nessas pesquisas. Por exemplo, a função pulmonar e a atopia foram fenótipos presentes no nosso estudo e em mais 3 estudos [FITZPATRICK et al. 2011, HOWRYLAK et al. 2014; LEE et al.

2017]. Estes resultados podem ter sido similares pelo fato de a asma alérgica ser mais prevalente na infância. Além disso, há uma pior evolução da função pulmonar comparada a asma não alérgica [JUST et al. 2014].

O início dos sintomas da asma foi descrito como um fenótipo no estudo de LEE et al. (2017) [LEE et al. 2017]. Esses autores demonstraram que asma de início tardio esteve associado a uma função pulmonar alterada [LEE et al. 2017]. Por outro lado, os nossos resultados mostraram que o início dos sintomas da asma não esteve associado com função pulmonar alterada (pacientes com FAO). O início dos sintomas da asma é difícil de comparar pois não existe um consenso na idade para determinar início precoce e tardio. Sendo assim, cada estudo classifica asma precoce e tardia com diferentes idades. No presente estudo, adotamos 2 anos idade como limite para asma precoce e tardia devido a menor calibre da via aérea nessa faixa etária [Ferry et al. 2014], enquanto outros autores adotaram 6 anos de idade [LEE et al. 2017].

7.3 Estudo dos fatores de risco para o desenvolvimento da FAO

O estudo dos fenótipos mostrou que a obstrução das vias aéreas é um dos fenótipos clínicos nas crianças e adolescentes com asma. Até onde temos conhecimento, o estudo da FAO é o primeiro a reportar a incidência e os fatores de risco para a FAO em crianças e adolescentes com asma, sendo difícil a comparação desses resultados com outros estudos. Embora alguns autores tenham estudado a evolução da função pulmonar da criança até a vida adulta, nenhum deles avaliou o desenvolvimento da FAO durante a infância [SEARS et al. 2003; MOORE et al. 2010; FIYZPATRICK et al. 2011, McGEACHIE et al.

2016; QUEIROZ et al. 2017, BUI 2017, SCHULTZ et al. 2018]. Nosso estudo acompanhou por 4 anos a evolução da função pulmonar de crianças e adolescentes com asma, sendo a FAO detectada durante o período de seguimento. O desenvolvimento da FAO nas crianças e adolescentes em nosso estudo iniciou-se em média, a partir dos 10 anos de idade. Nesse sentido, McGeachie et al. (2016) mostraram que crianças com asma que apresentam função pulmonar alterada aos 10 anos de idade terão menor VEF₁ e na vida adulta [McGEACHIE et al. 2016]. Conjuntamente, esses dados sugerem que a alteração da função pulmonar pode estar presente mesmo em crianças e adolescentes que estão em tratamento da asma.

Nossos resultados mostram que variáveis como idade, índice de massa corporal, hospitalização por asma e resposta ao broncodilatador estão associadas independentemente ao desenvolvimento da FAO. Entretanto, após ajuste com modelo de regressão logística, apenas as variáveis exacerbação frequente e asma *steps* 4-5 permanecem como fatores de risco para desenvolver a FAO. Estudos mostram que pacientes com exacerbações frequentes e asma grave apresentam maior inflamação pulmonar [BOBOLEA et al. 2015, MOGENSEN et al. 2019], e a inflamação pulmonar tem sido a hipótese mais aceita para a alteração da função pulmonar [LEZMI et al. 2018].

7.4 Estudo da avaliação física na obstrução fixa das vias aéreas

Na asma, pacientes com limitação ao fluxo aéreo podem apresentar aumento da sensação de dispneia e consequente ser sedentário [COOPER 2009]. Os nossos resultados mostram que a maioria dos adolescentes com asma

são sedentários, independente do grupo (FAO ou não-FAO). No nosso estudo, o pico do consumo de oxigênio (VO_2), coeficiente respiratório, ventilação minuto, carga de esforço, sensação de fadiga dos MMII e dispneia foram similares entre os grupos FAO e não-FAO. Villa et al. (2011), estudou a potência aeróbica em adolescentes com asma e mostrou que aqueles indivíduos com asma grave e moderada não apresentaram diferença na relação VEF_1/CVF e no VO_2 [VILLA et al. 2011]. Em concordância, os pacientes do nosso estudo e de Villa et al. (2010) apresentavam bom controle da asma no momento da avaliação. Nesse sentido, Vahlkvist et al. (2010) demonstraram que a diferença do VO_2 entre pacientes com asma poderia não acontecer pela alteração do VEF_1/CVF , mas sim pela falta de controle da doença, independentemente da gravidade [VAHLKVIST et al. 2010]. Visto conjuntamente, esses dados sugerem que a função pulmonar pode não influenciar no potencial aeróbico desde que o paciente esteja com bom controle da asma. Acredita-se que o aumento do potencial aeróbio aconteça pela melhora dos sintomas da doença com o uso dos medicamentos adequados [VAHLKVIST et al. 2010; BATEMAN et al. 2012].

Além da avaliação do potencial aeróbico, nós também avaliamos o nível de atividade física (NAF) por meio de acelerômetro. Os dados do acelerômetro mostraram semelhança no número total de passos e tempo em atividade física de intensidade moderada a vigorosa (AFMV) entre os grupos FAO e não-FAO. Previamente, alguns estudos avaliaram a AF em crianças e adolescentes com asma por meio do acelerômetro e descreveram a função pulmonar [SOUSA et al. 2014; REZNIK et al. 2018; MONTELL et al. 2016; WESTEGREN et al. 2017]. Igualmente aos nossos resultados, esses estudos mostraram similaridades no

número total de passos e tempo de AFMV em pacientes com diferentes padrões de função pulmonar [SOUSA et al. 2014; REZNIK et al. 2018; MONTELL et al. 2016; WESTEGREN et al. 2017]. Apesar da similaridade dos resultados desses estudos, nenhum deles definiu a obstrução da via aérea como irreversível. Sousa et al. (2014) e Reznik et al. (2018) mostraram que pacientes com função pulmonar alterada, medida pelo VEF_1/CVF menor que 0,80, não resultou em menor NAF [SOUSA et al. 2014; REZNIK et al. 2018]. Em comum, os pacientes desses estudos apresentaram bom controle da asma, o que contribuiu para melhorar o NAF [HASELKORN et al. 2010; VAHLKVIST et al. 2010; THAMRIN et al. 2011].

Atualmente, acredita-se que a FAO em adultos possa levar a hiperinsuflação dos pulmões, alterar a posição do diafragma que resulta numa desvantagem mecânica da força de contração do diafragma [ROCHA et al. 2017]. Embora adultos com FAO tendem a ter essa desvantagem mecânica, estudos em adolescentes com asma e baixo valor predito de VEF_1 apresentaram força muscular inspiratória similar a seus pares sem asma [OLIVEIRA et al. 2012; HEIZMANN et al. 2016]. Nesse sentido, nossos resultados mostraram similaridades da força muscular inspiratória entre os grupos. Infelizmente, nosso estudo não avaliou a hiperinsuflação pulmonar. No entanto, talvez a FAO nessa faixa etária não seja suficiente para causar retificação do diafragma e reduzir a força muscular inspiratória; isso porque, o pulmão na adolescência ainda está em desenvolvimento [McGEACHIE et al. 2016]. Interessantemente, em nosso estudo, os adolescentes do grupo FAO apresentaram maior força muscular expiratória quando comparada ao grupo não-FAO. Esse dado pode ter ocorrido,

pois pacientes com FAO necessitam de maior força dos músculos expiratórios para serem capazes de exalar o ar de dentro dos alvéolos. Como consequência, esses pacientes recrutam um maior número de células musculares para vencer a resistência das vias aéreas [DECRAMER et al. 1997].

Além dos músculos respiratórios, alguns estudos mostram que a musculatura periférica também pode apresentar diminuição da força muscular em pneumopatas [CANUTO et al. 2012; SOARES et al. 2010]. Lattorre-Romám et al. (2013) avaliaram a força de preensão palmar e mostraram correlação positiva com os valores de VEF_1 [LATORRE-ROMÁM et al. 2013]. Villa et al. (2011) avaliaram a força dos músculos do quadríceps, peitoral maior e grande dorsal, e os autores mostraram similaridade na força muscular entre os pacientes com função pulmonar normal e alterada [VILLA et al. 2011]. Em linha com os achados obtidos por Villa et al. (2011), nossos resultados mostraram que adolescentes com FAO e não-FAO também apresentam similaridade na força muscular dos MMSS e MMII. Além disso, vimos que a força muscular periférica não apresentou correlação com o VEF_1 . A diferença entre os nossos resultados e de Lattorre-Romám et al. (2013) é que no nosso estudo foram avaliados adolescentes com asma mais grave. Estudos mostram que pacientes com asma grave tendem a ingerir maiores doses de corticoide e consequentemente podem apresentar hipoxemia de tecidos celulares, pior nutrição muscular e baixa capacidade funcional [SOARES et al. 2010; MALAGUTI et al. 2011; LEVIN et al. 2014; RAMOS et al. 2015].

Nossos resultados mostram que adolescentes FAO e não-FAO apresentam semelhança nos escores de qualidade de vida, independentemente do domínio do questionário. Amaral et al. (2014) também mostraram similaridade nos domínios de qualidade de vida entre adolescentes com pico de fluxo expiratório, tanto menor, quanto maior ou igual a 80% do predito para a idade [AMARAL et al. 2014]. Por outro lado, estudos que avaliam pacientes com asma grave e não grave demonstram que função pulmonar alterada e qualidade de vida estão associados a asma grave [MONTELLA et al. 2016; NORDLUND et al. 2011]. A divergência desses resultados pode ter ocorrido devido ao controle da doença. Enquanto os pacientes dos estudos de Montella et al. (2016) e Nordlund et al. (2011) apresentavam asma parcialmente controlada ($C\text{-}ACT \leq 19$) [MONTELLA et al. 2016; NORDLUND et al. 2011], os pacientes do nosso estudo e do estudo de Amaral et al. (2014) apresentavam asma controlada ($\text{score} \geq 20$). Nesse sentido, o controle clínico da doença parece estar associado fortemente com melhor qualidade de vida nos pacientes com asma [AMARAL et al. 2014; PEREIRA et al. 2011]. Juniper et al. (2004) relata que o controle clínico dos sintomas, qualidade de vida e função pulmonar são componentes de saúde que devem ser avaliados [JUNIPER et al. 2004]. Sendo assim, o controle clínico informa sobre o tratamento da asma, enquanto a qualidade de vida informa sobre o bem-estar [JUNIPER et al. 2004]. Vistos conjuntamente, a qualidade de vida do adolescente com asma tem maior relação com o controle clínico da doença do que com a função pulmonar [AMARAL et al. 2014; PEREIRA et al. 2011; JUNIPER et al. 2004].

7.5 Implicações clínicas

Nossos dados sugerem que crianças e adolescentes com asma apresentam diferentes fenótipos clínicos; sendo assim, talvez cada paciente devesse ter o tratamento da asma individualizado com base nos fenótipos encontrados em nosso estudo. A busca pelo tratamento ideal da asma, seja farmacológico ou não farmacológico, é fundamental para que o controle da asma seja alcançado. Dessa forma, talvez seja possível evitar as exacerbações frequentes e a evolução para a asma grave; pois essas duas variáveis são os principais fatores de risco para a FAO. Apesar da FAO limitar o fluxo aéreo, essa alteração pode não ser suficiente para reduzir a prática regular da atividade física nos adolescentes com asma, uma vez que alguns pacientes com FAO no nosso estudo apresentaram bom condicionamento físico e bons níveis de atividade física de moderada a vigorosa. Sendo assim, acreditamos que estimular a atividade física mesmo em crianças e adolescentes, independente da presença de FAO, possa contribuir para o melhor manejo da asma.

7.6 Limitações

Este estudo tem algumas limitações. Primeiro, algumas variáveis do histórico pregresso da asma foi coletado por meio de perguntas aos responsáveis pelos pacientes, o que pode haver viés de memória por alguns entrevistados. Segundo, não foi analisado o fumo passivo das crianças e adolescentes; entretanto, todos os cuidadores dos pacientes com asma são orientados constantemente sobre a importância de não fumar perto das crianças e adolescentes com asma. Terceiro, a incidência da FAO em crianças e adolescentes com asma foi de 9,5%. A baixa incidência da FAO dificulta a

inclusão de várias variáveis para a análise de regressão logística múltipla. Quarto, o tamanho da amostra para comparar os grupos FAO e não FAO foi feita apenas para a variável VO_2 . Entretanto, a incidência da FAO na asma infantil é baixa, o que dificulta recrutar adolescentes com FAO para aumentar o tamanho da amostra. Quinto, o elevado nível do sedentarismo pode ter sido uma variável de confusão entre os grupos FAO e não FAO; entretanto, a maioria da população com asma no Brasil tem comportamento sedentário [Sousa et al. 2020]. Por último, a FAO foi detectada por meio da espirometria e não pelo teste de função pulmonar completo, o que poderia reportar o aprisionamento aéreo. Entretanto, o limite inferior da normalidade visto pela espirometria tem sido útil para detectar a FAO [ESCHENBACHER 2016].

8. Conclusão

Os fenótipos de crianças e adolescentes com asma são semelhantes aos de outros estudos de países desenvolvidos sendo apresentado por atopia, exacerbação da asma e função pulmonar alterada. Uma das alterações pulmonares que pode ocorrer na asma é a obstrução fixa das vias aéreas (FAO), e os fatores de risco para o desenvolvimento da FAO na infância foram a quantidade de exacerbações e a gravidade da asma (*steps* 4 e 5). Apesar da FAO limitar o fluxo aéreo, os pacientes com FAO demonstram semelhanças aos pacientes não-FAO quanto ao potencial aeróbio, o nível de atividade física, a força muscular periférica e a qualidade de vida.

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Apêndice**Anexo 1****Termo de Consentimento Livre e Esclarecido**

DADOS DE IDENTIFICAÇÃO DO SUJEITO DA PESQUISA OU
RESPONSÁVEL LEGAL

1.NOME:.....

DOCUMENTO DE IDENTIDADE Nº :

SEXO : M ☐ F ☐

DATA NASCIMENTO:/...../.....

ENDEREÇO:.....

Nº:.....COMPLEMENTO:.....BAIRRO:.....

CIDADE:.....ESTADO:.....

CEP:.....TELEFONE:(.....).....

2.RESPONSÁVEL

LEGAL:.....

NATUREZA (grau de parentesco, tutor, curador etc.):

.....

DOCUMENTO DE IDENTIDADE:.....

SEXO: M ☐ F ☐

DATA NASCIMENTO.:/...../.....

ENDEREÇO:.....

Nº:.....COMPLEMENTO:.....BAIRRO:.....

CIDADE:.....ESTADO:.....

CEP:.....TELEFONE:(.....).....

Dados sobre a pesquisa

1. TÍTULO DO PROTOCOLO DE PESQUISA: Avaliação do Nível de atividade física no paciente asmáticos com obstrução fixa das vias aéreas.
2. PESQUISADOR: Andrey Wirgues de Sousa
CARGO/FUNÇÃO: Fisioterapeuta INSCRIÇÃO CONSELHO REGIONAL Nº 87061
UNIDADE DO HCFMUSP: Programa de Pós Graduação em Clínica Médica.
3. AVALIAÇÃO DO RISCO DA PESQUISA:
RISCO MÍNIMO ☐ RISCO MÉDIO ☐
RISCO BAIXO X RISCO MAIOR ☐
4. DURAÇÃO DA PESQUISA: 2 anos.

Registro das explicações do pesquisador ao paciente ou seu representante legal sobre a pesquisa

Asma é uma doença pulmonar crônica, que se manifesta com episódios de tosse, chiado no peito e falta de ar. Apesar da asma ser estudada há anos pelos pesquisadores do mundo todo, muitas dúvidas ainda não foram solucionadas. Atualmente, sabemos que algumas pessoas asmáticas desenvolvem uma obstrução fixa no pulmão e que mesmo com a ajuda dos remédios, essa obstrução não é reversível. Esses pacientes são aqueles que possuem maiores chances de ter crises e internações de asma. Contudo, queremos saber se os pacientes asmáticos com essa obstrução fixa têm o mesmo nível de atividade física a aqueles pacientes que não possuem obstrução fixa.

O objetivo do nosso estudo é avaliar o seu nível de atividade física e juntamente com o de outras pessoas que tem asma.

Você está sendo convidado para participar do estudo, e caso aceite, você realizará um exame chamado Prova de Função Pulmonar aonde você irá respirar com a boca num filtro ligado a um computador e com clipe no nariz, isso para saber as capacidades e volumes do seu pulmão e identificar se há obstrução fixa. Logo após, você será convidado a comparecer ao Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), localizado na rua..... para algumas avaliações, que serão:

- Força muscular inspiratória: nessa avaliação, você irá colocar a boca num bocal limpo e irá puxar o ar com toda força que você conseguir. Você irá fazer isso por 3 vezes para que possa ser visto a maior força.
- Forma muscular dos braços: nessa avaliação, você irá levantar pesos com os braços para frente e para o lado do corpo. Você iniciará com um peso de 0,5kg sendo incrementado 0,5kg para cada vez que você consiga realizar o movimento.
- Força muscular das pernas: nessa avaliação, você irá se sentar num aparelho para realizar movimentos de abrir e fechar a perna além de fletir e estender o joelho. Você iniciará com um peso de 0,5kg sendo incrementado 0,5kg para cada vez que você consiga realizar o movimento.

Ao término das avaliações, você receberá um aparelho portátil (Acelerômetro) que pesa cerca de 34 gramas e serve para medir o nível de atividade física feita por você. O aparelho será colocado no pulso, igual a um relógio, e deve ser usado em tempo integral durante sete (7) dias, inclusive para dormir e tomar banho.

Após usar o aparelho por 7 dias, você retornará ao HCFMUSP para devolver o aparelho e realizar uma nova avaliação que será:

- Teste ergoespirométrico: esse é um teste força máxima onde você irá subir numa bicicleta e pedalar o máximo que você conseguir. No início você irá fazer um aquecimento de 3 minutos pedalando na bicicleta. Logo após, a bicicleta irá aumentar de carga, ficando assim mais difícil sua pedalada. A cada 2 minutos, a bicicleta aumentará de carga até você não conseguir mais pedalar. Nesse momento, o teste será interrompido e finalizado.

Após o teste você ficará sentado para descansar, caso você fique com falta de ar, os pesquisadores irão disponibilizar ajuda médica dentro do hospital para a sua total recuperação.

Nossa pesquisa oferece um baixo risco para você, sendo a falta de ar após o teste de esforço máximo ser o mais relevante, no entanto, os pesquisadores darão todo suporte possível para sua recuperação.

Caso quebre ou perca o aparelho, os responsáveis não arcarão com o prejuízo, porém pedimos que tome o máximo de cuidado porque temos poucos aparelhos disponível. Mesmo que o aparelho quebre, pedimos que o devolva.

A pesquisa não trará benefício e direto à você, porém, com o seu nível de atividade física estimado, nós poderemos dizer se você precisa melhorar ou manter o nível de atividade física para o bem estar da sua saúde.

Qualquer informação que você precise durante a pesquisa, você terá acesso aos profissionais responsáveis pela pesquisa no Hospital Infantil Darcy Vargas ou por telefone. O investigador principal é o Dr. Celso Ricardo Fernandes de Carvalho, que pode ser encontrado na Avenida Dr. Enéas de Carvalho Aguiar, 225, Cerqueira César, CEP: 05403-000 São Paulo-SP, telefone (11) 98415-3234. Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – Rua Ovídio Pires de Campos, 225 - 5º andar – tel: 3069-6442 ramais 16, 17, 18 ou 20, FAX: 3069-6442 ramal 26 – E-mail: cappesq@hcnet.usp.br

Você e seu responsável têm o direito de fazer qualquer pergunta sobre a pesquisa, de pensar com calma se quer ou não participar do estudo e de recusar a sua participação sem nenhum dano. Caso concorde em participar da pesquisa e posteriormente você queira desistir, você tem todo direito, sem que sofra nenhum tipo de prejuízo na sequência do seu tratamento dentro do Hospital Infantil Darcy Vargas.

As informações obtidas serão analisadas em conjunto com outros pacientes, não sendo divulgada a identificação de nenhum paciente, e somente os pesquisadores terão acesso. Os dados obtidos serão usados somente para essa pesquisa.

Você também terá o direito de ser atualizado sobre os resultados parciais da pesquisa.

Você e seu acompanhante não terão despesas pessoais em qualquer fase do estudo, incluindo as consultas e transporte. Não haverá também compensação financeira relacionada a sua participação no estudo. O seu transporte e de um acompanhante, nas duas visitas ao HCFMUSP serão custeados pelos pesquisadores. Vocês receberão o valor em dinheiro da passagem de transporte público (metrô e/ou ônibus) utilizado para ir até o hospital e voltarem para casa. O valor a ser pago do transporte público será o vigente na cidade de São Paulo – SP na época das visitas.

Informações do Pesquisador Executante:

Nome: Andrey Wirgues de Sousa.

Telefones: (11) 2308-3536 Celular: (11) 98782-3536

Endereço: Alameda Barros, n 142, apto 42, Santa Cecília, São Paulo-SP.

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo “Avaliação do Nível de atividade física no paciente asmáticos com obstrução fixa das vias aéreas”. Eu discuti com o Pesquisador Andrey Wirgues de Sousa, sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Assinatura do paciente/representante
legal

Data ____ / ____ / ____

Assinatura da testemunha

Data ____ / ____ / ____

para casos de pacientes menores de 18 anos, analfabetos, semianalfabeto ou portadores de deficiência auditiva ou visual.

(Somente para o responsável do projeto)

Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

Assinatura do responsável pelo estudo

Data ____ / ____ / ____

Anexo 2**Classificação do percentil de índice de massa corpórea conforme idade e gênero.**

Classificação	Faixa de percentil do IMC
Emagrecido	< 5
Eutrófico	≥ 5 e < 85
Sobrepeso	≥ 85 e < 95
Obeso	≥ 95

Anexo 3**Avaliação da força muscular**

Nome: _____ ID: _____

Data de nascimento: _____ Data da Avaliação: _____

	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	Média
PI _{máx} (cmH ₂ O)						
PE _{máx} (cmH ₂ O)						
Preensão palmar (Kgf)						
Extensor de joelho (Kgf)						

Anexo 4

Recomendações para o uso do aparelho

Nome: _____ ID: _____

Data de nascimento: _____ Data da Avaliação: _____

Data	Horário que acordou	Horário que dormiu	Observação

- Importante usar o aparelho o dia inteiro, retirando apenas para tomar banho, entrar na piscina e dormir.
- Se por algum motivo precisar retirar o aparelho por algum período, anote o horário que tirou e que colocou o aparelho novamente no diário!

CUIDADOS COM O APARELHO:

- Nunca esqueça de colocar o cinto **IMEDIATAMENTE** após o banho!
- Usar somente pano úmido para higienizar o aparelho, quando for necessário;
- Evitar molhar o aparelho e **NÃO** o deixar submerso na água!
- Nunca abrir o botão preto localizado do lado do aparelho;
- Deixar sempre o aparelho em contato com o corpo (não necessariamente com a pele).

Anexo 5

Preparo para o teste de esforço cardiopulmonar

- Realizar uma refeição leve 2 horas antes do exame.
- Não tomar bebidas a base de cafeína, como o café, chá, refrigerante e bebidas alcoólicas.
- Não comer chocolate.
- Não fumar no dia do exame.
- No dia do exame você deve levar roupas leves como short, camiseta, meia e principalmente TÊNIS.
- Trazer sua “bombinha” (Salbutamol) e espaçador, caso você tenha em casa.
- Trazer identidade do adolescente e comprovante de residência.

Anexo 6

Escala de Borg

Nome: _____ RGHC: _____

Data de nascimento: _____ Data da Avaliação: _____

Peso: _____ Estatura: _____ FC basal: _____ PA basal: _____

Borg basal dispneia: _____ Borg basal MMII: _____

Tempo (min)	FC	Borg dispneia	Borg MMII	PA
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				

Recuperação

Tempo (min)	FC	Borg dispneia	Borg MMII	PA
1				
2				
3				

Anexo 7

Childhood Asthma Control Test (C-ACT)

1. Como está sua asma hoje?

Pontuação:
(0) Muito Ruim	(1) Ruim	(2) Boa	(3) Muito Boa	

2. Sua asma é um problema quando você corre, faz exercícios, ou pratica algum esporte?

(0) É um grande problema, eu não consigo fazer o que eu quero	(1) É um grande problema e eu não gosto	(2) É um pequeno problema, mas tudo bem	(3) Não é problema

3. Você tosse por causa da sua asma?

(0) Sim, o tempo todo	(1) Sim, na maioria das vezes	(2) Sim, algumas vezes	(3) Não, nunca

4. Você acorda à noite por causa da sua asma?

(0) Sim, o tempo todo	(1) Sim, na maioria das vezes	(2) Sim, algumas vezes	(3) Não, nunca

PERGUNTAS PARA OS RESPONSÁVEIS

1. Nas últimas 4 semanas, quantas vezes seu filho teve sintomas de asma durante o dia?

(5)	(4)	(3)	(2)	(1)	(0)	Pontuação:
Nenhum	1 a 3 dias	4 a 10 dias	11 a 18 dias	19 a 24 dias	Todos os dias	

2. Nas últimas 4 semanas, quantas vezes seu filho apresentou chiado no peito por causa da asma?

(5)	(4)	(3)	(2)	(1)	(0)
Nenhum	1 a 3 dias	4 a 10 dias	11 a 18 dias	19 a 24 dias	Todos os dias

3. Nas últimas 4 semanas, quantas vezes seu filho acordou durante a noite por causa da asma?

(5)	(4)	(3)	(2)	(1)	(0)
Nenhum	1 a 3 dias	4 a 10 dias	11 a 18 dias	19 a 24 dias	Todos os dias

Pontuação Total:

CÁLCULO E RESULTADO DOS PONTOS:
 ≤ 19 PONTOS INDICA ASMA NÃO CONTROLADA.

Anexo 8

Questionário sobre a qualidade de vida na asma pediátrica com atividades padronizadas (PAQLQ)

QUESTIONÁRIO SOBRE A QUALIDADE DE VIDA NA ASMA PEDIÁTRICA COM ATIVIDADES PADRONIZADAS (PAQLQ(S))

AUTO-APLICADO (SELF-ADMINISTERED) PORTUGUESE VERSION FOR BRAZIL

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This translation has been made possible through a
grant from ASTRAZENECA R&D Lund
Translated by MAPI RESEARCH INSTITUTE
Senior Translator: Luiza Botelho Junqueira

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FEVEREIRO 2001

QUESTIONÁRIO SOBRE A QUALIDADE
DE VIDA NA ASMA PEDIÁTRICA (S)
(PORTUGUESE VERSION FOR BRAZIL)
AUTO-APLICADO

IDENTIFICAÇÃO DO PACIENTE _____

DATA _____

Página 1 de 5

Por favor, responda a **todas** as perguntas fazendo um círculo em volta do número que melhor descreve como você se sentiu **durante a última semana, por causa de sua asma.**

O QUANTO VOCÊ FOI **INCOMODADO/A** DURANTE A ÚLTIMA SEMANA AO:

	Extremamente incomodado/a	Muito incomodado/a	Bastante incomodado/a	Mais ou menos incomodado/a	Um pouco incomodado/a	Quase nada incomodado/a	Nem um pouco incomodado/a
1. Fazer ATIVIDADES FÍSICAS (como correr, nadar, praticar esportes, subir ladeira/morro ou escadas e andar de bicicleta, etc.)?	1	2	3	4	5	6	7
2. CONVIVER COM ANIMAIS (como brincar com animais de estimação ou tomar conta de animais, etc)?	1	2	3	4	5	6	7
3. Fazer ATIVIDADES COM SEUS AMIGOS E SUA FAMÍLIA (como brincar na hora do recreio ou fazer coisas com seus amigos e sua família)?	1	2	3	4	5	6	7
4. TOSSIR	1	2	3	4	5	6	7

EM GERAL, **COM QUE FREQUÊNCIA** DURANTE A ÚLTIMA SEMANA VOCÊ:

	O tempo todo	A maior parte do tempo	Frequen- temente	Algumas vezes	De vez em quando	Quase nunca	Nunca
5. se sentiu CHATEADO/A por causa de sua asma?	1	2	3	4	5	6	7
6. se sentiu CANSADO/A por causa de sua asma?	1	2	3	4	5	6	7
7. se sentiu PREOCUPADO/A OU ABORRECIDO/A por causa de sua asma?	1	2	3	4	5	6	7

QUESTIONÁRIO SOBRE A QUALIDADE
DE VIDA NA ASMA PEDIÁTRICA (S)
(PORTUGUESE VERSION FOR BRAZIL)
AUTO-APLICADO

IDENTIFICAÇÃO DO PACIENTE _____

DATA _____

Página 2 de 5

O QUANTO VOCÊ FOI **INCOMODADO/A** DURANTE A ÚLTIMA SEMANA POR?

	Extremamente incomodado/a	Muito incomodo- dado/a	Bastante incomodo- dado/a	Mais ou menos incomodo- dado/a	Um pouco incomodo- dado/a	Quase nada incomodo- dado/a	Nem um pouco incomodo- dado/a
8. CRISES / ATAQUES DE ASMA	1	2	3	4	5	6	7

EM GERAL, **COM QUE FREQUÊNCIA** DURANTE A ÚLTIMA SEMANA VOCÊ:

	O tempo todo	A maior parte do tempo	Freqüen- temente	Algumas vezes	De vez em quando	Quase nunca	Nunca
9. Sentiu RAIVA por causa de sua asma?	1	2	3	4	5	6	7

O QUANTO VOCÊ FOI **INCOMODADO/A** DURANTE A ÚLTIMA SEMANA POR?

	Extremamente incomodado/a	Muito incomodo- dado/a	Bastante incomodo- dado/a	Mais ou menos incomodo- dado/a	Um pouco incomodo- dado/a	Quase nada incomodo- dado/a	Nem um pouco incomodo- dado/a
10. CHIADO / CHIO NO PEITO	1	2	3	4	5	6	7

EM GERAL, **COM QUE FREQUÊNCIA** DURANTE A ÚLTIMA SEMANA VOCÊ:

	O tempo todo	A maior parte do tempo	Freqüen- temente	Algumas vezes	De vez em quando	Quase nunca	Nunca
11. se sentiu MAL- HUMORADO/A, IRRITADO/A por causa de sua asma?	1	2	3	4	5	6	7

O QUANTO VOCÊ FOI **INCOMODADO/A** DURANTE A ÚLTIMA SEMANA POR ?

	Extremamente incomodado/a	Muito incomodo- dado	Bastante incomodo- dado/a	Mais ou menos incomodo- dado/a	Um pouco incomodo- dado/a	Quase nada incomodo- dado/a	Nem um pouco incomodo- dado/a
12. APERTO NO SEU PEITO / PEITO TRANCADO	1	2	3	4	5	6	7

EM GERAL, **COM QUE FREQUÊNCIA** DURANTE A ÚLTIMA SEMANA VOCÊ:

	O tempo todo	A maior parte do tempo	Frequen- temente	Algumas vezes	De vez em quando	Quase nunca	Nunca
13. se sentiu DIFERENTE DOS OUTROS OU EXCLUÍDO/A por causa de sua asma?	1	2	3	4	5	6	7

O QUANTO VOCÊ FOI **INCOMODADO/A** DURANTE A ÚLTIMA SEMANA POR?

	Extremamente incomodado/a	Muito incomodo- dado/a	Bastante incomodo- dado/a	Mais ou menos incomodo- dado/a	Um pouco incomodo- dado/a	Quase nada incomodo- dado/a	Nem um pouco incomodo- dado/a
14. RESPIRAÇÃO CURTA	1	2	3	4	5	6	7

EM GERAL, **COM QUE FREQUÊNCIA** DURANTE A ÚLTIMA SEMANA VOCÊ:

	O tempo todo	A maior parte do tempo	Frequen- temente	Algumas vezes	De vez em quando	Quase nunca	Nunca
15. se sentiu CHATEADO/A POR NÃO CONSEGUIR ACOMPANHAR O RITMO DOS OUTROS?	1	2	3	4	5	6	7

EM GERAL, **COM QUE FREQUÊNCIA** DURANTE A ÚLTIMA SEMANA VOCÊ:

	O tempo todo	A maior parte do tempo	Frequen- temente	Algumas vezes	De vez em quando	Quase nunca	Nunca
16. ACORDOU DURANTE A NOITE por causa de sua asma?	1	2	3	4	5	6	7
17. NÃO SE SENTIU À VONTADE por causa de sua asma?	1	2	3	4	5	6	7
18. sentiu FALTA DE AR por causa de sua asma?	1	2	3	4	5	6	7
19. achou que NÃO CONSEGUIRIA ACOMPANHAR O RITMO DOS OUTROS por causa de sua asma?	1	2	3	4	5	6	7
20. DORMIU MAL DURANTE A NOITE por causa de sua asma ?	1	2	3	4	5	6	7
21. sentiu MEDO POR CAUSA DE UMA CRISE DE ASMA?	1	2	3	4	5	6	7

PENSE EM TODAS AS ATIVIDADES QUE VOCÊ FEZ DURANTE A ÚLTIMA SEMANA :

	Extremamente incomodado/a	Muito incomodo- ado/a	Bastante incomodo- ado/a	Mais ou menos incomodo- ado/a	Um pouco incomodo- ado/a	Quase nada incomodo- ado/a	Nem um pouco incomodo- ado/a
22. O quanto você foi incomodado/a por sua asma durante essas atividades?	1	2	3	4	5	6	7

EM GERAL, **COM QUE FREQUÊNCIA** DURANTE A ÚLTIMA SEMANA VOCÊ:

	O tempo todo	A maior parte do tempo	Freqüen- temente	Algumas vezes	De vez em quando	Quase nunca	Nunca
23. teve dificuldade para RESPIRAR FUNDO?	1	2	3	4	5	6	7

CÓDIGO DE ÁREA:

Sintomas: 4, 6, 8, 10, 12, 14, 16, 18, 20, 23

Limitação nas atividades: 1, 2, 3, 19, 22

Função emocional: 5, 7, 9, 11, 13, 15, 17, 21

Anexo 9

Prestação de contas
Processo CNPq Nº 311443/2014-1
Recibo de valores gastos com transportes de pacientes

Valores gastos com auxílio transporte de pacientes do Hospital das Clínicas de São Paulo para participação de protocolos de pesquisas com realização de avaliações físicas e exames complementares, realizados no Departamento de Fisiopatologia Experimental da Faculdade de Medicina da Universidade de São Paulo tendo como responsável o Prof. Dr. Celso Ricardo Fernandes de Carvalho.

Paciente:

Responsável legal pelo paciente:

RG:

CPF:

Endereço:

Tel.:

Valor recebido para a participação da pesquisa, referente a duas visitas ao Hospital das Clínicas. Ano de referência 2018: R\$20,00.

Assinatura do responsável

Anexo 10

Parecer consubstanciado do cep

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Fatores preditores para obstrução fixa das vias aéreas em crianças e adolescentes asmáticos

Pesquisador: Celso Ricardo Fernandes de Carvalho

Área Temática:

Versão: 2

CAAE: 54692116.7.0000.0065

Instituição Proponente: Faculdade de Medicina da Universidade de São Paulo

Patrocinador Principal: FUNDAÇÃO DE AMPARO À PESQUISA DO ESTADO DE SÃO PAULO
MINISTÉRIO DA CIÊNCIA, TECNOLOGIA E INOVAÇÃO

DADOS DO PARECER

Número do Parecer: 1.540.338

Apresentação do Projeto:

NA

Objetivo da Pesquisa:

NA

Avaliação dos Riscos e Benefícios:

NA

Comentários e Considerações sobre a Pesquisa:

Segundo relato.

O pesquisador respondeu adequadamente às nossas solicitações e explicitou o cálculo do tamanho amostral

Considerações sobre os Termos de apresentação obrigatória:

NA

Recomendações:

Aprovação

Conclusões ou Pendências e Lista de Inadequações:

Aprovado

Endereço: DOUTOR ARNALDO 251 21º andar sala 36

Bairro: PACAEMBU

CEP: 01.246-903

UF: SP

Município: SÃO PAULO

Telefone: (11)3893-4401

E-mail: cep.fm@usp.br

FACULDADE DE MEDICINA DA
UNIVERSIDADE DE SÃO
PAULO - FMUSP

Continuação do Parecer: 1.540.338

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_667913.pdf	27/04/2016 09:25:42		Aceito
Outros	RespostaRelator.docx	27/04/2016 09:22:31	Celso Ricardo Fernandes de Carvalho	Aceito
Outros	Referencias.docx	27/04/2016 09:20:28	Celso Ricardo Fernandes de Carvalho	Aceito
Projeto Detalhado / Brochura Investigador	Projeto.docx	27/04/2016 09:19:32	Celso Ricardo Fernandes de Carvalho	Aceito
Outros	CadastroDeProtocoloDePesquisa.pdf	31/03/2016 10:37:06	Celso Ricardo Fernandes de Carvalho	Aceito
Folha de Rosto	FolhaDeRosto.pdf	31/03/2016 10:34:03	Celso Ricardo Fernandes de Carvalho	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.docx	24/02/2016 16:52:08	Celso Ricardo Fernandes de Carvalho	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

SAO PAULO, 11 de Maio de 2016

Assinado por:

Maria Aparecida Azevedo Koike Folgueira
(Coordenador)

Endereço: DOUTOR ARNALDO 251 21º andar sala 36

Bairro: PACAEMBU

CEP: 01.246-903

UF: SP

Município: SAO PAULO

Telefone: (11)3893-4401

E-mail: cep.fm@usp.br

Outras atividades relevantes

1) Colaboração em projetos de pesquisa no grupo “Liffe”:

- “Efeito da associação dos exercícios aeróbios e respiratórios no controle clínico e aspectos psicossociais de pacientes com asma moderada a grave”, sob o número de protocolo 4616/17/116, da pós-graduanda Fabiane Sera Kim.
- “Efeitos de um programa de condicionamento físico com o método pilates sobre o controle clínico e a qualidade de vida de pacientes com asma”, sob o número 57515416.0.00000.0068, da pós-graduanda Marília Graziella de Oliveira Carneiro.

2) Participação como autor na revisão sistemática que está sendo feita pelo grupo “Liffe” com o título: *Effect of adding motivational interventions to physical training on physical activity and sedentary behavior in patients with chronic respiratory diseases*. Número de registro no PROSPERO: CRD42020162921.

3) Apresentar de trabalhos científicos no *European Respiratory Congress*:

- Apresentação de um trabalho no formato de pôster em **Milan 2017** com o tema (*Perceived barriers to physical activity in asthmatic children*).
- Apresentação de dois trabalhos sendo um no formato discussão de pôster e outro em pôster em **Paris 2018** com os temas (*Aerobic fitness in adolescents with asthma and fixed airway obstruction*, e *Risk factors*

for frequent asthma exacerbation in children and adolescents, respectivamente).

- Apresentação de dois trabalhos no formato de pôster em **Madri 2019** com os temas (*The influence of asthma characteristic in the aerobic fitness of adolescents* e *Can good aerobic fitness prevent asthma exacerbation in adolescents during the cold seasons?*).

4) Publicação de artigo como primeiro autor:

- Sousa AW, Cabral ALB, Martins MA, Carvalho CRF. *Barriers to daily life physical activities for Brazilian children with asthma: a cross-sectional study*. J Asthma. 2020 Jun;57(6):575-583.

Barriers to daily life physical activities for Brazilian children with asthma: a cross-sectional study

Andrey Wirgues Sousa, Anna Lúcia Barros Cabral, Milton Arruda Martins & Celso R. F. Carvalho

To cite this article: Andrey Wirgues Sousa, Anna Lúcia Barros Cabral, Milton Arruda Martins & Celso R. F. Carvalho (2019): Barriers to daily life physical activities for Brazilian children with asthma: a cross-sectional study, Journal of Asthma, DOI: [10.1080/02770903.2019.1594249](https://doi.org/10.1080/02770903.2019.1594249)

To link to this article: <https://doi.org/10.1080/02770903.2019.1594249>

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Barriers to daily life physical activities for Brazilian children with asthma: a cross-sectional study

Andrey Wirgues Sousa, MSc^a, Anna Lúcia Barros Cabral, MD, PhD^b, Milton Arruda Martins, MD, PhD^c, and Celso R. F. Carvalho, PhD^a

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BACKGROUND

Objective: To identify barriers to daily life physical activities (DLPA) and to evaluate physical activity levels for children with asthma and without asthma.

Method: This is a cross-sectional study that enrolled 130 children with asthma and 54 non-asthma, from 7 to 12 years old. All of the children in both groups used an accelerometer for 6 consecutive days to assess DLPA and completed a questionnaire to evaluate barriers to physical activity. Accelerometer was used to measure each child's total number of steps, as well as the number of steps and the time spent in moderate-to-vigorous physical activity (MVPA). The barrier questionnaire to DLPA included 11 questions, divided into three domains: personal, social and environmental.

Results: The most commonly described barrier to DLPA in the asthma and non-asthma groups was an unsafe environment (23.6% vs 28.5%, respectively). The asthma group reported having asthma (19%) and lack of parental encouragement (17.3%) as being other important barriers to DLPA. It was also observed that the asthma and non-asthma groups presented similar values for the total number of steps ($13,379 \pm 3,837$ vs $14,055 \pm 3,914$, respectively, $p > 0.05$), number of steps in MVPA ($5,654 \pm 1,988$ vs. $6,025 \pm 2,058$, $p > 0.05$), and time spent in MVPA (46 ± 16 min vs. 50.8 ± 14.7 min, $p > 0.05$).

Conclusions: An unsafe environment is the main barrier to physical activity for Brazilian children. Moreover, a lack of parental encouragement and having asthma were considered to be barriers to physical activity. And lastly, children have similar levels of physical activity whether they have asthma or do not have asthma.

ARTICLE HISTORY

Received 25 May 2018
Revised 9 February 2019
Accepted 8 March 2019

KEYWORDS

Accelerometer; sedentary lifestyle; weather conditions; unsafe environment

Introduction

Asthma is the most common chronic inflammatory disease of the airways and is characterized by episodes of wheezing, dyspnea, chest tightness and coughing, most commonly at night [1]. These symptoms may occur at rest or may be triggered by exercise; the fear of inducing breathlessness inhibits many patients from taking part in regular exercise [2]. Although exercise can induce dyspnea, the regular practice of exercise leads to several benefits, such as the improvement of aerobic capacity and health-related quality of life, as well as a reduction in dyspnea, the consumption of inhaled corticosteroids, the number of exacerbations and the intensity of exercise-induced bronchoconstriction [3–5]. Consequently, current international asthma guidelines suggest that individuals with asthma should be encouraged to remain physically active (i.e., perform 150 min of moderate-to-vigorous physical activity per week) [1].

Despite the benefits of regular daily life physical activity (DLPA) for people with asthma, there is evidence that most children with asthma do not perform the recommended minimal amount of DLPA [6,7]. Therefore, it seems relevant to understand the reasons why children, especially children with asthma, are physically inactive [8]. The barriers that inhibit DLPA are multifactorial including personal, social and environmental features, and can change according to the characteristics of different diseases [9]. There are few studies that evaluate barriers to DLPA in children. A recent systematic review suggests that children with motor or intellectual disabilities report a greater number of barriers to DLPA as compared to children without disabilities [10]. In addition, most studies that evaluated barriers to DLPA were qualitative [10]. To the best of our knowledge, there are only two studies that evaluate barriers to DLPA in children with asthma [11,12]. Fereday et al. (2009) performed a

quantitative study evaluating the barriers to DLPA in children with chronic illnesses including cystic fibrosis, type 1 diabetes and asthma [11]. The authors reported that these children did not perceive their diseases as barriers; however, children with asthma reported avoiding DLPA outdoors during the winter [11]. Glazebrook et al. (2006) also evaluated barriers for children with asthma and, in contrast to the observations made by Fereday and coworkers, the Glazebrook study showed that children with asthma, and their parents, perceived asthma as a barrier to DLPA [12]. The study also showed that children with asthma presented lower physical activity levels and more overweight, compared to their non-asthma peers [13,14].

Considering that children with asthma may be less physically active than their non-asthma peers, [13] and that regular exercise leads to a better clinical condition [3], it is necessary to understand the barriers to DLPA for these children. The purpose of this study was to identify barriers to DLPA and to evaluate the physical activity levels of children with asthma and children without asthma.

Methods

Participants

This cross-sectional study included 184 children of both sexes, from 7 to 12 years of age, of which 130 were on-going outpatient children with asthma and 54 were children without asthma (non-asthma group). The children with asthma had been diagnosed in accordance with the *Global Initiative for Asthma* (GINA) [1]. The children were recruited during a regular medical visit to a University tertiary hospital, from 2014 to 2015. The children with asthma in the study had been under optimal medical treatment for at least 12 months, were clinically stable (i.e., Children Asthma Control Test ≥ 20) and had not presented any exacerbations or changes in medication for at least 30 days. Asthma severity was classified according to the treatment required to achieve good asthma control according to GINA [1]. Briefly, this means that children in steps 1 and 2 required a low daily dose of an inhaled corticosteroid (ICS), those in step 3 required a low daily dose of an ICS associated with a long-acting beta₂-agonist (LABA), and children in steps 4 and 5 required a moderate or high daily dose of an ICS associated with a LABA. The exclusion criteria for the asthma group were: the presence of any pulmonary, cardiovascular, neurological or musculoskeletal disease that might interfere in the practice of exercise.

The inclusion criteria for the non-asthma group were: the absence of asthma and/or rhinitis (International Study of Asthma and Allergy (ISAAC) score ≤ 5) [15], and the absence of any pulmonary, cardiovascular, neurological or musculoskeletal diseases. The non-asthma group consisted of 43 (79.6%) cousins and/or neighbors of the children in the asthma group and 11 (20.4%) children of employees of the university hospital. To avoid bias during comparisons, the children in the non-asthma group were recruited proportionately with the asthma group utilizing group (or frequency) matching [16] according to three categories: sex (male or female), age group (7–8, 9–10, 11–12 years old), and body mass index (either eutrophic or overweight/obese).

The Hospital Ethics Committee approved the study and written informed consent was obtained from the patients and their parents. The researcher covered the cost of transportation for all of the children and their parents, and no financial compensation was offered for participation in the study.

Study design

Study participants underwent two evaluations at the hospital, 7 days apart. During the first hospital visit, all of the children underwent anthropometric analysis that included age, sex, weight, height and body mass index (BMI). Only the asthma group performed the lung function test and c-ACT. The non-asthma group completed the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire to exclude any participants with symptoms of asthma, rhinitis and eczema. Utilizing group matching, the non-asthma group participants were recruited from children of hospital employees as well as from cousins and/or neighbors of study participants in the asthma group. Then, all of the children received an accelerometer and were instructed to use it for 6 consecutive days, including week and weekends. During the second visit, all of the children returned the accelerometers and answered the questionnaire on barriers to DLPA. For both the asthma and non-asthma groups, the data from the accelerometers and the information from the completed questionnaires on barriers to DLPA were evaluated by the same researcher.

Anthropometrical data

Weight

Weight was measured using a digital scale with a precision of 0.1 kg (Toledo, Brazil) and the children wore minimal clothing and no shoes.

Height

Height was measured in meters (m) using a stadiometer with a precision of 0.1 cm (Toledo, Brazil).

Body mass index (BMI)

BMI was expressed as kg/m^2 and presented in comparison to the median BMI percentile. Children were classified as overweight or obese if their BMI equaled or exceeded the age-adjusted cutoff point (≥ 85 th percentile), while normal weight was defined as a BMI below the age-adjusted cutoff point (< 85 th percentile) [17].

Assessments

Barriers to DLPA questionnaire

Participants were evaluated using the questionnaire described by Martins [18], and questions were divided into three domains: personal, social and environmental/geographic, as described by Leslie et al. [19]. Barriers in the personal domain included muscle discomfort, lack of interest, time constraints and not knowing how to exercise. Barriers in the social domain included a lack of the following: parental encouragement, company, equipment and financial resources. Barriers in the environmental domain included an unsafe environment, weather conditions and lack of infrastructure. For each barrier, participants were asked to select one of five responses: “never”, “rarely”, “sometimes”, “almost always” or “always.” Situations were considered to be barriers when the participant selected the options “always” or “almost always”. Domains were also compared. A domain was considered to be a factor that hampered physical activity when the participant selected either the option “always” or “almost always” for, at least, 50% of the barriers in any domain. Having asthma was included in the questionnaire in the personal domain. All participants responded to the questionnaire without parental interference. The barriers to physical activity were the primary outcomes, and the domains were considered secondary.

Daily life physical activity (DLPA)

Daily life physical activity (DLPA) was quantified using an accelerometer (Power Walker-610, Yamax, Japan). The device measures the total number of steps and the number of steps and the time spent engaged in moderate to vigorous physical activity (MVPA, ≥ 110 steps per minute) [20,21]. All of the children enrolled in the study, and their caregivers were instructed that the accelerometer should be put on

every child each morning and removed only to bathe and sleep. In addition, the children were instructed not to change their habitual DLPA while using the device. To be considered physically active, a child's accelerometer had to register ≥ 60 min per day of MVPA; otherwise, the child was classified as physically inactive [22].

Lung function test

The technical procedure, eligibility criteria and reproducibility were established as recommended by the American Thoracic Society [23]. The spirometer (Koko DigiDoser, Louisville, Kentucky, USA) was coupled with a microcomputer, and the following parameters were evaluated: forced expiratory volume in the 1st second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC . Spirometry was performed before and after the inhalation of 400 μg of salbutamol to measure the percentage of the bronchodilator response.

ISAAC questionnaire

This questionnaire evaluates asthma and rhinitis symptoms; the score ranges from 0 to 14 points and is translated to and validated in Portuguese [24]. The absence of asthma symptoms was defined by a total score ≤ 6 . The children completed the questionnaire with assistance from their parents or guardians [25].

Childhood asthma control test (c-ACT)

Asthma control was classified as controlled, partly controlled or uncontrolled, in accordance with GINA guidelines [1]. Asthma control was defined by the presence/absence of daytime symptoms, limitation of activities, nocturnal symptoms/awakening, need for rescue treatment, and FEV_1 . The c-ACT assessed asthma control during the 4 weeks prior to the first hospital visit evaluation and the results were then translated to, and validated in, Portuguese [26]. The c-ACT questionnaire had seven questions regarding asthma symptoms and the effect of asthma on daily functioning. The first four questions were answered by the children, and the last three were answered by their parents. Each question had four options for the children, from 0 (worst) to 3 (best) and 6 options for parents, from 0 (worst) to 5 (best). Possible scores ranged from 0 (totally uncontrolled asthma) to 27 (totally controlled asthma); scores ≥ 20 represented good asthma control [27]. Permission was obtained to use the c-ACT questionnaire.

Statistical analysis

The number of children recruited for the study was based on a convenience sample according to the inclusion criteria. The data collected were analyzed using the Statistical Package for Social Science (SPSS) software, version 17.0 (Chicago, IL). The Kolmogorov-Smirnov normality test was used to determine if a data set was correlated with a normal distribution model. Data from the total number of steps, as well as steps and time in MVPA, were evaluated using a Student's *t* test. The Chi-square test was used to evaluate the frequency of the barriers reported by the children and to compare group matching strata. The level of statistical significance was set at 5% for all tests ($p < 0.05$), and the power was set at 80%.

Results

A total of 221 children were invited to participate in the study, and 184 of them were selected to be included in the study. One hundred thirty children with asthma were assigned to the asthma group, and 54 children without asthma were assigned to the non-asthma group (Figure 1). In the asthma group, participants were classified in accordance with the step definition of their asthma: steps 1 or 2 ($n = 57$), step 3 ($n = 42$) and steps 4 or 5 ($n = 31$). In both the asthma

and the non-asthma groups, there were more boys than girls. Other than that, there were no significant differences between the two groups relative to age, height, weight and BMI ($p > 0.05$, Table 1). Most of the children in the asthma and non-asthma groups were classified as physically inactive (respectively, 73.8% and 65.8%, Table 1). The total number of steps, the number of steps and time spent in moderate-to-vigorous physical activity (MVPA), were similar for the asthma and non-asthma groups (Table 1).

The number of barriers reported in each group was similar. Most of the children reported up to 1 barrier in both the asthma and non-asthma groups (65% and 59%, respectively), and a lower percentage in both groups reported ≥ 2 barriers (35% and 41%, respectively). It was also observed that children who perceived no more than one barrier to DLPA were more physically active than those children who perceived ≥ 2 barriers (78% vs 25%, respectively, $p = 0.01$, Figure 2). In both groups, the total numbers of steps recorded for obese and non-obese children were similar; however, the MVPA of obese children was lower than the MVPA of non-obese children (Table 2).

The three most commonly reported barriers (60%) in the asthma group were an unsafe environment, having asthma and lack of parental encouragement (Table 3). In the non-asthma group, the three most commonly reported barriers (70.2%) were unsafe

Figure 1. STROBE diagram of the study participants.

Table 1. Anthropometric, lung function and daily life physical activity data of the asthma and non-asthma groups.

	Asthma (130)	Non-asthma (54)	<i>p</i>
Anthropometric data			
Sex, male (%)	90 (68)	31 (57)	0.75
Age, years	9 ± 1.75	9 ± 1.74	0.66
Height, meters	1.40 ± 0.10	1.40 ± 0.11	0.89
Weight, kilograms	37.5 ± 9.9	36.9 ± 11.2	0.75
BMI, percentile	59 ± 32.5	65.8 ± 27.9	0.22
Overweight / obese (%)	40 (31)	19 (35)	0.44
Lung function			
FVC, % of predicted	98.4 ± 10.1	–	
FEV ₁ , % of predicted	87.2 ± 10.3	–	
% of change post BD	27.2 ± 15.6	–	
mL of change post BD	417.5 ± 225.9	–	
FEV ₁ /FVC	0.80 ± 0.08	–	
c-ACT			
Mean score	23 ± 2.5	–	
Daily Life Physical Activities			
Total number of steps	13,379 ± 3,837	14,055 ± 3,914	0.45
Number of steps in MVPA	5,654 ± 1,988	6,025 ± 2,058	0.41
Minutes spent in MVPA	46 ± 16	50.8 ± 14.7	0.31
Percentage of physically inactive children	73.8	65.8	0.36

Legend: Data are presented in mean and standard deviation, except where noted (gender, overweight/obese and percentage of physically inactive children). BMI: body mass index; FVC: forced vital capacity; FEV₁: forced expiratory volume in 1st second; BD: bronchodilator; mL: milliliters; c-ACT: children-asthma control test; MVPA: moderate-to-vigorous physical activity.

Figure 2. Reporting rate of physically active and physically inactive children according to the number of barriers. In both groups, children who perceived lower barriers presented more physical activity. Chi-squared statistical test was used; *statistical significance: $p < 0.05$.**Table 2.** Total number of steps taken, number of MVPA steps taken, and amount of time spent in MVPA, by the obese and non-obese children in the study.

	Non-obese (125)	Obese (59)	<i>p</i>
Total number of steps	13,625 ± 4,571	12,874 ± 4,054	0.28
Number of steps in MVPA	6,284 ± 1,145	5,894 ± 1,210	0.03
Minutes spent in MVPA	48.8 ± 13	44 ± 12.2	0.02

Legend: Data are presented as mean and standard deviation. Children with a Body Mass Index ≥ 85 were classified as obese. MVPA: Moderate-to-vigorous physical activity; Step and minutes measurements represent an average total amount per day based on measurements over a 6-day period.

Table 3. Perceived barriers to daily physical activities among the asthma and non-asthma groups.

	Asthma (130)	Non-asthma (54)	<i>p</i>
Reported barriers			
Unsafe environment	31 (23.6)	16 (29.6)	0.66
Having asthma	25 (19)	–	–
Lack of parental encouragement	23 (17.3)	3 (7.1)	0.16
Lack of infrastructure	20 (15.2)	11 (20.3)	0.48
Weather conditions	18 (13.7)	11 (20.3)	0.24
Time constraints	17 (12.9)	10 (19)	0.8
Lack of company	14 (10.6)	8 (14.8)	0.72
Lack of interest	12 (9.1)	10 (19)	0.14
Muscle discomfort	10 (7.6)	3 (5.5)	0.77
Lack of equipment	9 (6.8)	6 (11.1)	0.45
Not knowing how to exercise	8 (6.1)	4 (7.1)	0.91
Lack of financial resources	1 (0.7)	3 (5.5)	0.29

Legend: The barriers are listed in order of decreasing importance as reported by the group with asthma. The order of importance is different for the two groups, except for the most important barrier reported by both groups: an unsafe environment. The other barriers were reported in similar proportion by both the asthma and non-asthma groups ($p > 0.05$); *N* = number of children.

Figure 3. Reporting rate of the domains that hamper physical activity. In both groups, the environmental domain is what most hampers the physical activity. Chi-squared statistical test was used; *statistical significance: $p < 0.05$.

environment, lack of infrastructure and weather conditions (Table 3). The individual barriers reported by the children were proportionately similar in both the asthma and non-asthma groups. (Table 3, $p > 0.05$). The lack of parental encouragement as barrier to physical activity was reported by 17.3% of the asthma group, and by 7.1% of the non-asthma group, a finding of no significant difference (Table 3, $p > 0.05$).

The environmental domain was the most reported domain in both the asthma and non-asthma groups. No significant difference was observed between the asthma and the non-asthma groups, in the personal (7% vs 13%, respectively, $p = 0.15$), social (7% vs 11%, respectively, $p = 0.320$) and environmental (33% vs 29%, respectively, $p = 0.54$) domains (Figure 3).

Discussion

The present study shows that an unsafe environment, having asthma and lack of parental encouragement were the main barriers to DLPA for children with asthma. In addition, the environmental domain was perceived as the main barrier to DLPA for children in both the asthma and non-asthma groups. Moreover, children that reported no more than one barrier to DLPA have higher levels of physical activity than children who reported two or more barriers. And lastly, children in the asthma and non-asthma groups presented similar levels of physical activity.

An unsafe environment was the most commonly reported barrier to DLPA for both the asthma and non-asthma groups. This could have occurred because the study was conducted in the city of São Paulo, Brazil, a megalopolis in a developing country. As a consequence, children may prefer to stay at home, or they may be advised by their parents to do so [28,29]. This may explain why most children were physically inactive. Our study is supported by previous studies reporting that even healthy young children living in a megalopolis in developing countries avoid outdoor physical activities when they perceive the environment as unsafe [30]. Although an unsafe environment can be a difficult barrier to overcome because it depends on public policies, a reduction in physical inactivity can be achieved with simple actions such as increasing the number of parks or the opening of schools on weekends [30,31]. These steps can be important considering physical inactivity has been demonstrated to be a public health problem and economic burden [32].

The second most important barrier to DLPA reported by the asthma group was having asthma (Table 3). To our knowledge, there are only two studies that evaluate asthma perception as a barrier to DLPA [11,12]. Glazebrook et al. showed that children from the United Kingdom reported having asthma (66%) as the main barrier to DLPA [12]. In contrast, for Australian children with asthma, Fereday et al. showed that having asthma was not a barrier to performing DLPA [11]. Several factors could explain the difference between both studies, such as asthma severity and asthma control. Children with asthma in the present study as well as in the Fereday study [11] had good asthma control. In the Glazebrook study, however, asthma control was not reported [12], probably because the children in that study were evaluated prior to the initiation of clinical treatment. This difference could help explain why a majority of the children with asthma from Glazebrook's study [12]

reported having asthma as a major barrier to DLPA. Interestingly, 19% of the children in our study reported having asthma as a barrier, despite having good asthma control (ACT score ≥ 20). A probable explanation could be related to previous experience with asthma symptoms during DLPA prior to achieving good asthma control [33].

The third most reported barrier to DLPA in the asthma group was lack of parental encouragement (Table 3). This result may suggest that parents fear their children will experience asthma symptoms if they engage in physical activity, even though the children's asthma is well-controlled. In Glazebrook's study [12], 60% of the patients reported a lack of parental encouragement, which is 3.4 times higher than the percentage observed in our study (17.3%). It is difficult to compare the results between our study and Glazebrook's study [12]; however, we hypothesize three possible explanations for this difference. First, the children assessed by Glazebrook et al. (2006) did not present good asthma control, which could explain their parents' fear of encouraging them to engage in physical activity [12]. Second, Glazebrook et al. (2006) [12] evaluated children in the United Kingdom, where the climate is generally colder than the climate in Brazil. Children with asthma in the U.K. may experience more exercise-induced bronchoconstriction due to increased exposure to the colder climate [34]. Third, children with asthma present several phenotypes, which can complicate analyses of children from different countries [35].

It is interesting to note that weather conditions and lack of infrastructure were two of the five barriers to DLPA reported by both the asthma and non-asthma groups. Our data are supported by a previous study suggesting that weather conditions can reduce DLPA [36]. Although weather conditions cannot be controlled, their relevance as a barrier to DLPA can be reduced by public policies that promote the construction of indoor recreational facilities in communities [37,38]. This is even more important for children with asthma as dry weather, cold temperatures and pollution can provoke an increase in airway hyperresponsiveness [39,40]. In the city of São Paulo, the largest megalopolis in South of America, high levels of air pollution occur frequently and can exacerbate these triggers [41].

Previous studies have suggested that children with asthma are more physically inactive than their non-asthma peers [42]. However, other studies have shown that children with asthma who are clinically stable present similar physical activity levels to those of their peers [43,44]. In the present study, most of the

children in both the asthma and non-asthma groups were physically inactive (73.8% vs 65.8%, respectively). The physically inactive children reported a higher number of barriers to DLPA and were proportionately more obese than the physically active children. These results are supported by a previous study, which showed that most physically inactive children with asthma are obese [45]. Puglisi et al. reported that obese children without asthma reported a higher number of barriers to DLPA than the non-obese children without asthma [46]. In the present study, no difference was observed in the number of barriers to DLPA reported by obese and nonobese children in the asthma and non-asthma groups (data not presented). Physical inactivity can lead to obesity [47], and this is particularly relevant in children with asthma because it increases asthma symptoms and worsens asthma control [47,48]. Taken together, these findings suggest that physical inactivity is multifactorial and cannot be reduced solely by appropriate medical treatment.

Our study has limitations. First, there is no standardized, specific instrument to evaluate barriers to DLPA in children. Therefore, we used a previously validated questionnaire for adults [18]. In our opinion, this was not a problem because the children were able to respond to all of the questions in the questionnaire. Second, the perception of a barrier is subjective, and it can be either over or underestimated [49]. However, we observed that children in both the asthma and non-asthma groups reported a similar number of barriers, which suggests that asthma itself did not influence the children's perceptions. Finally, the matching process is a difficult task; however, we believe that matching patients based on anthropometrical characteristics and socioeconomic status was done appropriately and adequately as no significant differences were observed between groups. It was also observed that families presented similar incomes. The fact that both groups reported an unsafe environment as the main barrier to DLPA suggests that both groups had a similar socioeconomic status.

Conclusion

Children with asthma and children without asthma present similar physical activity levels. The main barrier to physical activity for both groups is an unsafe environment. Having asthma, and a lack of parental encouragement, are also considered barriers to physical activity by most of the children, even by children with good asthma control. These results can be useful

for developing interventions to improve physical activity in children with asthma.

Acknowledgements

The authors acknowledge the cooperation of the university hospital that made this study possible. In addition, they thank the children and the families who participated in this study.

Declaration of interest

The protocol was submitted to, and approved by, the Ethics Committee of the University and the parents or legal guardians of the children gave their written, signed consent for their participation in the study. All the authors declare that no grants, gifts, equipment or drugs were provided by any company for this study or for any participant. Also, no tobacco company funded or was involved in any part of this study or manuscript. Any unexpected adverse effects or changes in protocols have been disclosed. The main author had access to the entire manuscript and takes full responsibility for the integrity and accuracy of the data.

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