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Exercise-induced respiratory symptoms in childhood

PhD Thesis submitted by

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Foreword

The main aim of my PhD was to study exercise-induced respiratory symptoms in children in Switzerland. For that purpose, I helped build a national clinical cohort study of children referred to paediatric respiratory outpatient clinics in Switzerland, the Swiss Paediatric Airway Cohort (SPAC). As I started my PhD in April 2016, the SPAC study was still on the drawing board, and it took more than one year to get the ethical approval, prepare study documents, develop the digital database, organise the recruitment in the different hospitals and begin recruiting patients for the cohort. During the development phase and while waiting for the SPAC study to accumulate data, I worked with two existing databases, the Leicestershire Respiratory Cohort study (LRC) and the Avon Longitudinal Study of Parents and Children (ALSPAC), to validate a previously developed tool to predict childhood asthma. This project was an important part of my PhD project as it introduced me to the topic of respiratory symptoms in childhood, and it taught me how to plan, analyse, report, and publish a research project. However, in this PhD thesis, I will focus mainly on the work related to exercise-induced respiratory symptoms using data from the SPAC study, and the results from the first validation study will be part of the results and will briefly be discussed but not described in the introduction nor in the methods.

In this PhD thesis I focus on children and adolescents aged 0-17 years, however for simplicity, I will use the term “children” when referring to individuals aged 0-17 years and the term “adolescents” when referring to individuals aged 13-17 years.

1 Abstract

Background Exercise-induced symptoms (EIS) are common in childhood and can lead to physical activity avoidance, reduced quality of life, and overtreatment with inhaled corticosteroids if mistakenly diagnosed as asthma. Diagnosis of EIS can be difficult because different aetiologies share similar clinical presentations. Reported symptoms can be helpful to identify the correct diagnosis, as certain symptoms are typically associated with specific diagnoses (e.g. expiratory wheeze for exercise-induced bronchoconstriction, and throat tightness for inducible laryngeal obstruction (ILO)). Only few studies have investigated diagnosis, diagnostic evaluations, and reported symptoms in children with EIS.

Aims: The overall aim of this PhD thesis were to gain epidemiological knowledge about diagnosis, diagnostic investigations, and reported symptoms in children with EIS. Specifically, I aimed to 1) set up a prospective study including children referred to paediatric respiratory outpatient clinics with respiratory symptoms 2) study diagnosis, diagnostic investigations and management in children referred for EIS 3) study if parent reported EIS are helpful to distinguish different diagnoses and 4) study EIS reported by physicians in the clinical history and assess agreement with parent-reported symptoms. 5) Additionally, I aimed to validate a model to predict asthma in preschool children.

Methods: To address the aims of this PhD thesis, I used data from the Swiss Paediatric Airway Cohort (SPAC), a longitudinal observational clinical study of children referred with respiratory symptoms to paediatric respiratory outpatient clinics in Switzerland. I used data from medical records to get information on referral diagnosis, final diagnosis, diagnostic investigations and proposed management from the outpatient clinics. I used data from parental questionnaires to get information about symptoms. For publication 5, I used data from the Leicestershire Respiratory Cohort (LRC) and the Avon Longitudinal Study of Parents and Children (ALSPAC).

Results: The main body of this thesis consists of 5 articles (2 published, 1 in review, and 2 to be submitted). These are the main findings in summary:

Publication 1: The SPAC study is a novel longitudinal observational cohort study of children with respiratory symptoms. By January 7, 2020, the SPAC study includes 1893 children

recruited from 10 pulmonology clinics. The SPAC study will provide real-life data from paediatric pulmonology clinics in Switzerland and will serve as a platform for nested studies.

Publication 2: Diagnosis given at the paediatric respiratory outpatient clinic differed from suspected referral diagnosis in half of the children referred primarily for EIS. Dysfunctional breathing was a common diagnosis at the outpatient clinic but rarely suspected at time of referral. Diagnostic evaluation, management, and follow-up were inconsistent between clinics and diagnostic groups.

Publication 3: Parent reported EIS (including information on type of symptoms, activities triggering EIS, and characteristics of symptoms) can help to distinguish different diagnoses in children seen with EIS.

Publication 4: Physicians reported EIS in the medical records in almost all children referred for EIS. Activities triggering EIS and characteristics of EIS (e.g. localisation of symptoms, respiratory phase, and onset and duration of symptoms) were reported only in around half of the children. Agreement with parent questionnaire reported EIS ranged from poor to moderate.

Publication 5: PARC predicted asthma at school age equally well in the validation cohort, ALSPAC (AUC 0.77), compared with the development cohort, LRC (AUC 0.78). Apart from severity of wheeze and cough, family history of symptoms, age, and sex, also exercise as trigger for respiratory symptoms predicted asthma at school age in the development and validation cohort. The discriminative ability of the PARC appeared to be robust to changes in inclusion criteria, scoring variables, and outcome definitions. PARC may need recalibration when applied in other populations.

Additionally, I contributed to further publications, which are included in this PhD thesis as related publications.

Conclusion

In summary, diagnosis, diagnostic investigations, and management in children with EIS differed between outpatient clinics and diagnosis groups, indicating a need for diagnostic guidelines. Parental reported symptoms can help to distinguish diagnoses in children with EIS. Future studies should focus on developing an algorithm for diagnosing children seen with EIS including both reported symptoms and objective diagnostic tests.

2 Abbreviations

ALLIANCE	All Age Asthma Cohort
ALSPAC	Avon Longitudinal Study on Parents and Children
AUC	Area under the curve
DB	Dysfunctional breathing
CLE	Continuous laryngoscopy exercise test
EIB	Exercise-induced bronchoconstriction
EILO	Exercise-induced laryngeal obstruction
EIS	Exercise-induced Symptoms
ENT	Ear, nose, throat
FeNO	Fraction of exhaled nitric oxide
GERD	Gastroesophageal reflux
GINA	Global Initiative for Asthma
ICS	Inhaled corticosteroids
ILO	Inducible laryngeal obstruction
ISAAC	International Study of Asthma and Allergies in Childhood
ISPM	Institute of Social and Preventive Medicine
k	Kappa
LABA	Long acting beta agonist
LRC	Leicestershire Respiratory Cohort
MAS-90	Multicentre Allergy Study
PARC	Predicting Asthma Risk in Children
R^2	R-squared
SABA	Short acting beta agonist

SHAPE	Hyperventilation Syndrome Ambroise-Paré Enfant
SPAC	Swiss Paediatric Airway Cohort

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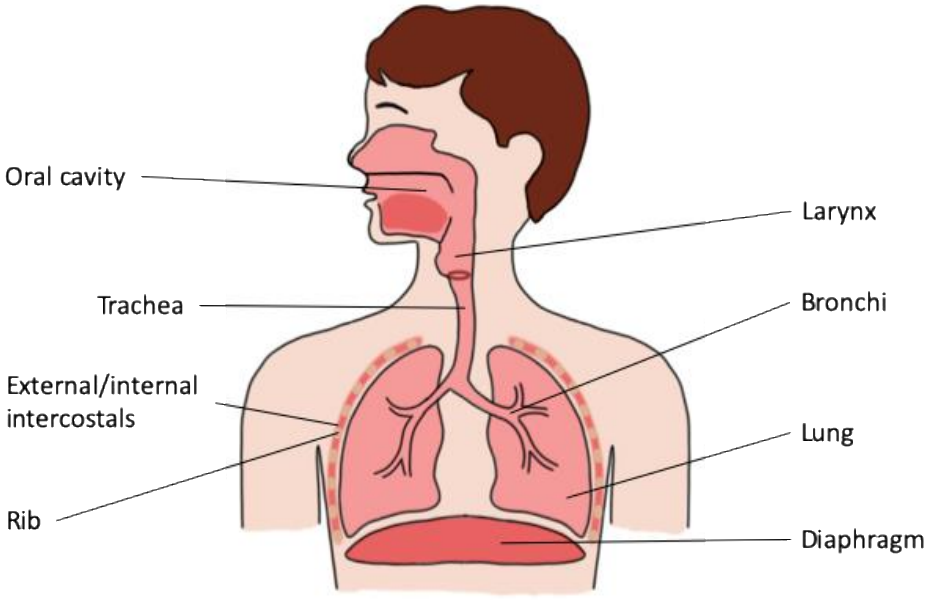
4 Introduction

4.1 The respiratory system

The purpose of the respiratory system is to provide an optimal environment for exchange of gases (oxygen and carbon dioxide) between the air and the pulmonary blood. The respiratory system comprises the upper respiratory tract (oral cavity and larynx), the lower respiratory tract (trachea, bronchi and lungs), and the muscles involved in breathing (diaphragm and intercostal muscles) (**figure 1**). The respiratory system can be subdivided into the extrathoracic part including the upper respiratory tract and the thoracic part including the lower respiratory tract and the muscles involved in breathing.

Figure 1: Anatomy of the respiratory system



4.2 The respiratory system during exercise

During exercise, the demand for gas exchange increases dramatically. In a moderately fit person, oxygen consumption can rise from 300 ml per minute during rest to 3000 ml per minute during intensive exercise (1). The increased oxygen demand leads to an increase in heart rate, breathing rate and depth of breathing. For a given exercise-intensity, the ventilation demand is higher in children than in adults (2).

4.3 Exercise-induced respiratory symptoms in children

Some children experience symptoms as a response to the increased demand on the respiratory system during exercise. These symptoms are referred to as exercise-induced symptoms (EIS). The most common symptoms triggered by exercise are dyspnoea or breathlessness, whistling breathing sounds (including expiratory wheeze or inspiratory stridor), chest- or throat tightness, or cough. Chest pain, quick fatigability, and dizziness are also frequent complains during exercise (3-5). EIS are triggered by varying types of activities. Strenuous activities such as biking fast, running fast, swimming, or intensive sport games (e.g. basketball) are commonly reported as triggers of EIS (6, 7). Additionally, winter sports such as cross country skiing can also induce EIS (8, 9).

4.4 Prevalence of EIS in children

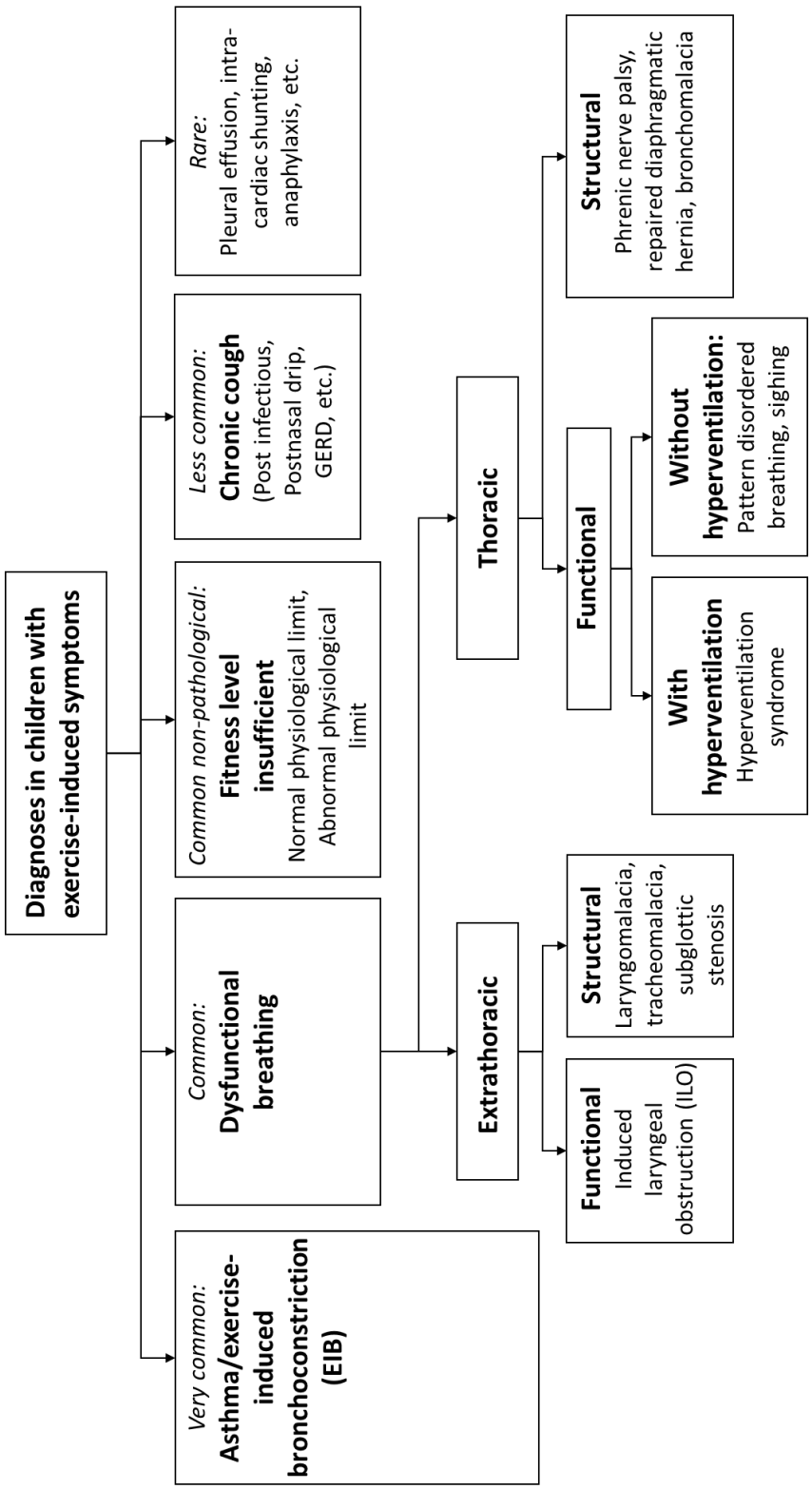
The prevalence of EIS in the general paediatric population has been estimated in different studies. The International Study of Asthma and Allergies in Childhood (ISAAC) study measured prevalence of questionnaire reported asthma-related exercise-induced symptoms from data collected between 1991 and 1995 in 155 countries worldwide (10). Wheeze during or after exercise in the past 12 months was globally reported by 6% (regional range: 3 to 15%) of children aged 6 to 7 years, and by 19 % (regional range: 10 to 39%) of adolescents aged 13 to 14 years. Data from the ISAAC phase 3 study using data collected in 2001 to 2003 showed that the prevalence of wheeze during or after exercise had not changed for children aged 6 to 7 years with a global prevalence of 6% (regional range: 4-15%) in children aged 6-7 years but had increased slightly in adolescents aged 13 to 14 years with a global prevalence of 19% (regional range: 7 to 38%) (11). The ISAAC study included no questions about exercise-induced cough or dyspnoea. A UK study in 2025 adolescents aged 14-17 from the general population found that 26% reported exercise-induced cough (12). A Swedish population-based study assessed the prevalence of EIS using data collected in 2011 from 2309 adolescents aged 12 to 13 years and found that 330 (14%) answered yes to the question “Have you ever had an attack of shortness of breath that happened after strenuous activity at any time during the last 12 months?” (3). Symptoms other than shortness of breath and symptoms that occurred during exercise (as opposed to after activity) were not captured with this question. In summary, these studies that the prevalence of EIS in the

general population of children is relatively high, but the estimated prevalence depends on geographical area and the wording of the question used to measure EIS.

4.5 Causes of exercise-induced respiratory symptoms in childhood

The most common cause of EIS is exercise-induced bronchoconstriction (EIB) occurring in children with or without diagnosed asthma. Other frequent causes of EIS are dysfunctional breathing, insufficient fitness level, and chronic cough (13, 14). In rare cases, EIS can be a manifestation of serious pulmonary or non-pulmonary causes such as pleural effusion, intracardiac shunting or anaphylaxis. The causes of exercise-induced respiratory symptoms are schematically described in **figure 2**. Iron deficiency and anaemia can also cause EIS and should be considered when pulmonary or cardiac causes have been ruled out. Because iron deficiency is a rare cause of EIS in children and mainly seen in adult athletes, it is not described in detail here (13). This PhD thesis focuses on the most common causes of EIS seen in children with exercise induced respiratory problems. I describe these causes separately below including information on definition, pathophysiology, signs and symptoms, diagnosis, management, and epidemiology.

Figure 2: Schematic illustration of diagnoses in children with exercise-induced symptoms adapted from Barker et al. (15)



4.5.1 Exercise-induced bronchoconstriction (EIB)

EIB is defined as an acute narrowing of the lower airways triggered by exercise (16, 17). The mechanism causing EIB is complex and yet not clear. Thermal- and osmolality changes in the airway surface are thought to play a dominant role in triggering EIB. During exercise, large amounts of air are humidified before entering the alveoli which can cause water loss of the airway surface, trigger smooth muscle contraction, and cause bronchoconstriction (18, 19). EIB mainly occurs in children with asthma but can also occur in children with no asthma symptoms apart from during exercise (20).

The most common symptoms of EIB are cough, wheezing, and chest tightness (3, 21, 22). Dyspnoea also occurs in children with EIB but usually in combination with other symptoms; isolated dyspnoea is suggestive of other causes of EIS (23). Children with EIB also present with symptoms such as increased fatigue and chest pain. Symptoms are commonly associated with expiration and are worst 3-15 minutes after ending exercise, and symptoms last from 10 to 30 minutes if untreated (24).

The diagnosis of EIB is based on objective diagnostic tests in addition to and not only on reported symptoms, as reported symptoms alone have shown to poorly predict responses to objective tests (25). The optimal method for diagnosing EIB is exercise-challenge testing with lung function measurements performed before and after exercise (4). Direct challenge tests using either methacholine or histamine are also used for diagnosing EIB but have shown lower sensitivity and specificity to diagnose EIB than the indirect test with exercise (26). Most commonly, running on treadmill is used for exercise-challenge as it more easily provokes EIB in children than cycling (27). Free running has been shown to provoke EIB better than treadmill running, but it is difficult to standardize the workload using free running, which is important for optimal sensitivity and specificity of the test (28, 29). In patients with asthma-symptoms triggered not only by exercise, spirometry and a bronchial reversibility test is usually performed as the first diagnostic test before exercise-challenge testing (30).

The goal of the management of EIB is to get symptoms under control. (16). The most recent report from the Global Initiative for Asthma (GINA) recommends the use of short acting beta agonists (SABA) in combination with inhaled corticosteroids (ICS) or long acting beta agonists (LABA) as the first step in the management of EIB (31).

EIB is common in children from the general population with an estimated prevalence of 2-23% (measured with exercise-challenge test) (32-36). The prevalence of EIB is higher in children with asthma with estimated prevalence of up to 90% (35, 37, 38) and in children participating in sports at elite levels with prevalence between 35-40% (39, 40).

4.5.2 Dysfunctional breathing

Dysfunctional breathing is an umbrella term for disorders characterised by abnormal breathing patterns that are often triggered by exercise. Dysfunctional breathing in childhood can occur in absence of or in addition to asthma. No agreement exists in the literature of the definition of dysfunctional breathing and which disorders are covered by the term, but several authors have described characteristics and classifications of dysfunctional breathing. In this PhD thesis, I base the definition of dysfunctional breathing on work done by Barker et al, and Depiazzi et al. (15, 41). They proposed to define dysfunctional breathing as "an alteration in the normal biomechanical patterns of breathing that result in intermittent or chronic symptoms which may be respiratory and/or non-respiratory" (15). They divide dysfunctional breathing into thoracic (dysfunctional breathing which may or may not be associated with hyperventilation) and extra-thoracic dysfunctional breathing (involvement of the upper airway). Thoracic and extra-thoracic dysfunctional breathing are then further divided into functional and structural dysfunctional breathing (**figure 2**). Structural dysfunctional breathing involves anatomical and neurological abnormalities, where functional dysfunctional breathing involves no component of anatomical or neurological abnormality. Connet and Thomas describe dysfunctional breathing more simply as abnormal dysfunctional breathing patterns that are either thoracic or laryngeal in nature (42).

In the following part I describe extrathoracic and thoracic dysfunctional breathing disorders separately.

4.5.2.1 Extrathoracic dysfunctional breathing

The majority of children with EIS caused by extrathoracic dysfunctional breathing have inducible laryngeal obstruction (ILO), which is mostly functional. Only few have EIS due to

structural extrathoracic dysfunctional breathing such as laryngomalacia or subglottic stenosis.

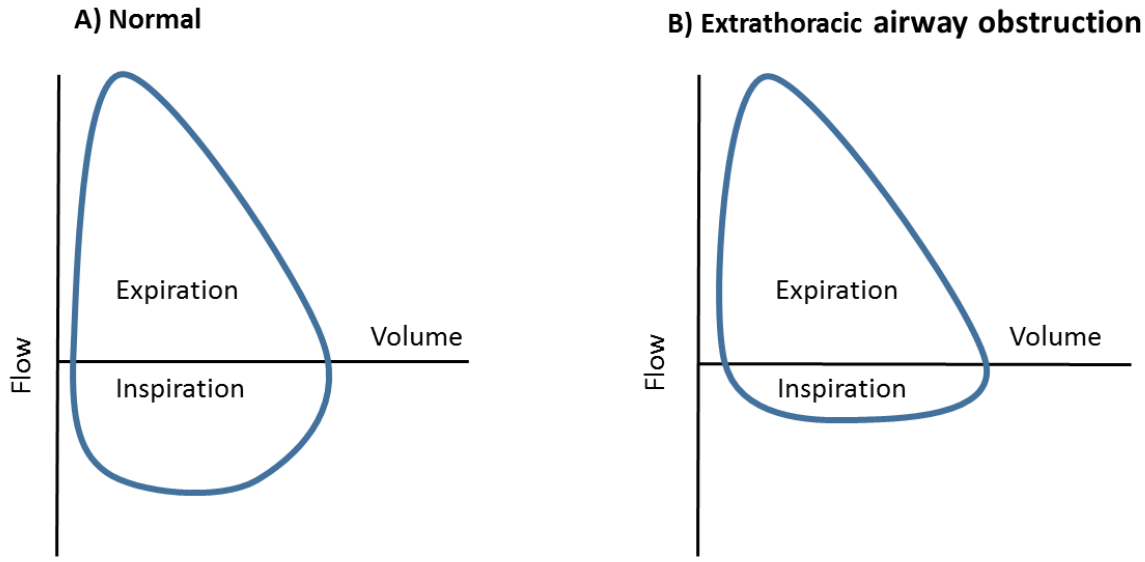
Inducible laryngeal obstruction (ILO)

ILO is defined as different conditions characterised by narrowing of the glottic and/or supraglottic structures. ILO can be triggered by different external factors but exercise is the most common trigger (20, 43). In the past, ILO has been described using different terms (e.g. paradoxical vocal fold motion, laryngeal dyskinesia, exercise-induced laryngomalacia, and vocal cord dysfunction) but the ILO was recently proposed as an umbrella term for all conditions involving paroxysmal and episodic laryngeal closure (44). The term exercise-induced laryngeal obstruction (EILO) is sometimes used if symptoms are only triggered by exercise (45). In this PhD thesis, I use the broadest definition of ILO. The pathophysiology of ILO has not yet been fully understood, but several hypotheses about mechanisms have been proposed (46). During exercise, the larynx abduct maximally to facilitate maximal ventilation. In some individuals the laryngeal structures are smaller, which can limit air flow during excessive exercise despite maximal abduction of the larynx. Another mechanism may be weakened supraglottic structures which, in combination with dysfunctional laryngeal muscle activity, causes an inward collapse of the glottic or supraglottic structures (43).

A patient with ILO typically presents with shortness of breath, increased respiratory effort, throat tightness, and inspiratory stridor (47, 48). Less common are symptoms such as chest tightness, expiratory wheeze, and a dry cough (49). Symptoms usually begin shortly after starting exercise, peak during exercise and resolve fast after ceasing exercise. Patients usually report little effect of short acting beta agonist treatment (SABA). Diagnostic investigations in children suspected of ILO include spirometry, exercise-challenge test, and flexible continuous laryngoscopy exercise test (24). Spirometry during rest can provide information about truncated inspiration on the flow-volume loop, which can be suggestive of extrathoracic obstruction (**figure 3**) (50, 51). However, a normal flow-volume loop does not rule out ILO, as many children with ILO only experience symptoms during exercise (52). Also, an abnormal flow-volume loop can be the cause of inadequate instruction, suboptimal effort and inability to perform the required manoeuvre (50). The continuous laryngoscopy during exercise is considered the reference standard for diagnosing ILO. It allows video

assessment of the laryngeal movement during exercise and is used to detect abnormal degree of adduction of the larynx (48).

Figure 3: Schematic illustration of normal flow-volume curve (A) and a flow-volume curve showing truncated inspiration caused by extrathoracic airway obstruction (B)



The first step in the management of ILO is informing the patient of the condition and its benignity (48). Physiotherapy has been shown to reduce symptoms and anxiety in patients and should therefore be proposed to patients with ILO (53, 54). Psychotherapy can be helpful in patients whose symptoms are triggered by psychologically stressful situations (55, 56). In severe structural cases, surgical intervention may be necessary.

The prevalence of ILO in the adolescent general population is not well known. Only two studies measured the prevalence of EILO using flexible laryngoscopy during exercise in adolescents aged 12-24 and found prevalence between 5-7% (49, 57). Most children diagnosed with ILO are above 10 years of age (58). The prevalence of ILO is higher among athletes (59), and more females than males are affected (46, 54).

Laryngomalacia

Laryngomalacia is congenital abnormality of the laryngeal cartilage, which causes collapse of the supraglottic structures during inspiration (60). It is the most common cause of stridor in infants. In most cases, symptoms resolve within the first two years of life, but some children continue to have symptoms later on. A Norwegian study in 23 13-year-old adolescents who were diagnosed with laryngomalacia as infants found that 11 reported dyspnoea during exercise (61). Fourteen showed abnormal movement of mainly supraglottic structures during flexible laryngoscopy during exercise. Children with laryngomalacia as infants may have EIS later in childhood and this cause of EIS should not be overlooked although laryngomalacia is a rare cause of EIS in the general population.

Subglottic stenosis

Subglottic stenosis is a narrowing of the subglottic laryngeal structures, which is a rare structural cause of EIS (15, 62). Most often, subglottic stenosis is caused by scaring after prolonged intubation but can also be a rare congenital defect. Little data exist on the association between EIS and subglottic stenosis. An American study in 30 patients with mean age 28 (ranged 12-67 years), referred to a laryngology clinic for ILO found that 14 had exercise-induced symptoms and of these, three were diagnosed with subglottic stenosis (63).

4.5.2.2 Thoracic dysfunctional breathing

Thoracic dysfunctional breathing can be divided into functional and structural causes. Structural causes are rare and will not be described in detail in this PhD thesis. Functional thoracic dysfunctional breathing is also described as breathing pattern disorders (BPD), an umbrella term for different types of abnormal breathing patterns including hyperventilation, chronic upper-chest breathing, sighing tics, and habitual cough (64, 65). BPDs are complex and often not well-defined and sometimes include somatoform syndromes that can cause physical symptoms. The mechanisms involved in BPDs are complex and involve often a combination of functional and psychological aspects leading to dysfunctional breathing

patterns (66). In the following part, I shortly describe different types of BPDs including upper-chest breathing/hyperventilation syndrome, sighing tics, and habitual cough.

Upper-chest breathing/Hyperventilation syndrome

Upper-chest breathing is characterised by breathing with little activation of the diaphragm. Instead breathing is driven by the upper chest wall muscles (intercostal muscles) and accessory muscles (sternomastoid, upper trapezius, neck muscles, etc.) (67). This can lead to mild hyperinflation, irregular rate and volume of respiration. In some patients this dysfunctional breathing pattern leads to hyperventilation (15). Hyperventilation is defined as a respiration in excess of metabolic demands and can cause reduced arterial pCO_2 and subsequently increased pH (alkalosis) (68). Children with hyperventilation experience attacks of increased respiratory rate triggered by psychologically stressful situations (69). The clinical diagnosis of primary hyperventilation syndrome is made based on reported symptoms and diagnostic tests when organic disease has been excluded (70). Cardiopulmonary exercise test with measurements of end-tidal carbon dioxide can be used to diagnose hyperventilation syndrome (71).

The prevalence of hyperventilation in adolescents have been reported in 5-6% measured with a Nijmegen questionnaire score of >22 as suggestive of hyperventilation (72, 73). However, the Nijmegen questionnaire was not designed for assessing the prevalence of hyperventilation in adolescents and the validity for this purpose is not clear (74). A French study in 300 children aged 1-17 years used the Hyperventilation Syndrome Ambroise-Paré Enfant (SHAPE) questionnaire to assess hyperventilation and found a prevalence of 21% (75). Hyperventilation appears to be more prevalent in girls than boys and appear more often in adolescence than early childhood (72, 75).

Sighing tics

Sighing tics or sighing dyspnoea is characterised by a single or few irregular repetitive deep breaths (66). The frequency of the tics is variable and in some cases tics are accompanied by yawning. Symptoms mainly occur during rest but can occur during exercise, in which the common complaints are shortness of breath and chest tightness. Episodes can be triggered

by emotional stress and be accompanied by anxiety. Sighing tics are diagnosed based on reported and observed symptoms and the treatment is based on patient education about the condition and psychotherapy can be helpful in some cases (76). Sighing tics is an uncommon isolated cause of exercise-induced dyspnoea in children but may not be uncommon in combination with other causes of EIS. In a study in 52 children referred to a specialised pulmonology clinic for uncontrolled asthma, 14 (27%) were diagnosed with vocal cord dysfunction or sighing dyspnoea (77).

Habitual cough

Habitual cough is characterised by recurrent barking-like dry coughs that cannot be explained by organic disease such as infection or asthma (65). The cough is commonly not disturbing the patient itself, it does not cause the patient to wake up at night, and the patient can reproduce the cough if asked. Uncomfortable situations, including in some cases exercise, can trigger attacks of habitual cough (76). There is little knowledge of the prevalence of habitual cough, but prevalence has been reported between 5-30% in patients seen for cough lasting more than 4 weeks (78, 79). However, others report habitual cough to be uncommon in children (80). Patients with habitual cough are mostly below 18 years, and seems to affect males and females equally often (81).

4.5.3 Insufficient fitness level

Insufficient fitness level, also described as deconditioning, is used to describe different physical presentations related to EIS. Insufficient fitness level refers to a lower than expected physiological limit to exercise (abnormal physiological limit) caused by prolonged illness or sedentary behaviour, which leads to a reduction in the maximal oxygen uptake and reduced cardiac output during exercise (15). Insufficient fitness level also refers to individuals with complaints of breathlessness and increased fatigue with no restriction in maximal oxygen uptake during exercise (normal physiological limit) (**figure 2**). It has been shown that the perception of breathlessness during exercise varies between individuals, which might explain why some individuals perceive breathlessness as an abnormal response to exercise, while others do not (82).

The main complaints among children with insufficient fitness level are breathlessness and quick fatigability during exercise (13, 41). Insufficient fitness level is diagnosed using cardiopulmonary exercise test which measures the functional capacity of the pulmonary, cardiac and skeletal muscle system (83, 84).

The prevalence of insufficient fitness level as cause of EIS in children is not well known in the general paediatric population. A few studies have reported on diagnoses given to children referred for EIS to specialised pulmonary clinics. In a study in 142 children and young adults aged 6-21 years referred for EIS not suspected to be asthma, 74 (52%) were diagnosed with normal physiologic response to exercise (85). In a similar study in 79 children referred for EIS not suspected to be asthma, 7 (9%) were diagnosed with poor conditioning, while 53 (67%) were diagnosed with normal physiological response to exercise (86). Another study in 52 children with poorly controlled asthma and EIS, 12 (23%) were diagnosed with poor physical fitness (77). These studies show that insufficient fitness level is a frequent cause of EIS in children seen in specialised pulmonary clinics for exercise-related problems. Insufficient fitness level is more common among obese children (87, 88).

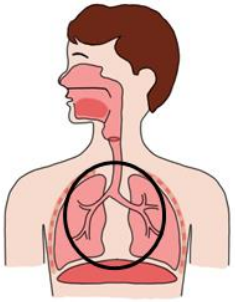
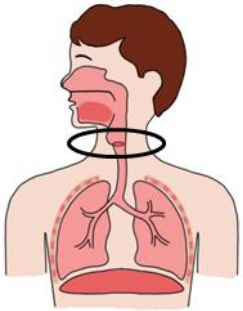
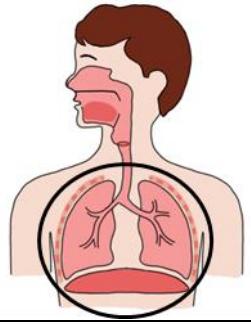
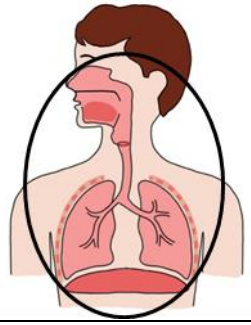
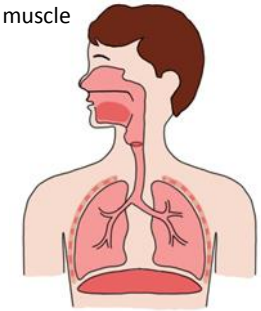
4.5.4 Chronic cough

Cough is a commonly reported symptom during exercise (5), and is defined as chronic when it persists longer than four weeks (89). The most frequent causes of cough during exercise are EIB (section 4.4.1) and extrathoracic dysfunctional breathing (section 4.4.2.1), but other aetiologies also cause cough during exercise including post nasal drip, postinfectious cough, and gastroesophageal reflux (GERD) (90). Upper airway cough syndrome (also referred to as post nasal drip) cause drainage of secretions into the pharynx, which can cause cough (91). Upper airway infections can cause cough, and in some patients coughing persist longer than three weeks following an upper airway infection, which is defined as postinfectious cough (92). In some patients, postinfectious cough is mainly triggered by exercise. Gastroesophageal reflux (GERD) can in some individuals be induced by exercise and cause cough (93). The diagnosis of chronic cough during exercise is considered after ruling out EIB and extrathoracic dysfunctional breathing and based on reported symptoms, objective tests, and in some cases treatment trials. Management depends on the cause of cough.

4.6 Differentiating the diagnoses related to EIS

It can be difficult to differentiate diagnoses in children presenting with EIS because clinical presentations partly overlap. Certain symptoms are, however, more commonly seen for some diagnoses than others. **Table 1** describes typical presentations in children with EIS by different aetiologies. Despite typical presentations for specific diagnoses, some children experience atypical symptoms (e.g. throat tightness in children with asthma, or symptoms during expiration in children with ILO). No single objective test serves as a reference standard for the different diagnoses related to exercise-induced symptoms in children, and reported symptoms therefore become especially important in diagnosing EIB. It is therefore difficult and time consuming to identify the correct diagnosis in these children, which can lead to delayed diagnosis or even misdiagnosis (94-96). Few papers describe diagnostic approaches to differentiate diagnoses in children with EIS. Niggemann describes the approach to differentiating organic diseases from functional or psychogenic diseases (97). He emphasizes the importance of asking the patients about clinical history and describe symptoms in detail including information on whether symptoms occur during inspiration/expiration, are accompanied by sounds (wheeze, stridor), occur during certain times of the day, occur at night or at rest, occur in the context of respiratory tract infections, limit sport activities, last for short or long, recover fast or slowly, are sensed in the throat or the chest, disappear with use of pharmacotherapy, are accompanied by tingling lips or fingers. Weiler et al. (16) described the approach to identify differential diagnoses in patients with EIS; If another diagnosis is suspected after performing relevant lung function tests to diagnose EIB (spirometry, bronchial challenge tests), differential diagnoses such as ILO should be considered. A key sign for considering differential diagnoses, apart from non-pathological objective test results, is failure to respond to asthma management. They suggest to perform laryngoscopy which can identify findings suggestive of ILO, laryngomalacia or GERD. They suggest to perform cardiopulmonary exercise test to identify if hyperventilation or deconditioning is causing EIS. They also suggest to refer children to an appropriate specialist (e.g. cardiologist, pulmonologist) if EIS are accompanied by chest pain, which might be suggestive of severe disease.

Table 1: Typical findings of common causes of EIS including symptoms, diagnostic tests, and treatment

Typical findings	EIB	Extrathoracic DB	Thoracic DB	Chronic cough	Fitness level insufficient
Symptoms	Dyspnoea, cough, wheeze, chest tightness, easy fatigability	Dyspnoea, throat tightness, stridor	Dyspnoea, sighing, chest pain, dizziness, tingling sensation in fingers/lips	Cough, throat clearing	Dyspnoea, easy fatigability or less endurance than peers
Respiration phase	Expiration mostly	Inspiration mostly	Expiration and inspiration	Expiration and inspiration	Expiration and inspiration
Timing of symptoms	During or after exercise	During exercise, at onset	During exercise	During exercise	During exercise
Duration of symptoms	10-60 minutes	Minutes	Minutes	Minutes to hours	Minutes to hours
Typical localisation of symptoms as reported by patients	Bronchi 	Larynx 	Thorax 	ENT, bronchi 	Cardiovascular, skeletal muscle 
Common diagnostic tests and results	Lung function • ↓ FEV1 after exercise-challenge • ↓ FEV1 after methacholine-challenge • ↑ FEV1 after bronchodilator • Variable occurrence of symptoms during exercise-challenge	Lung function • Variable inspiratory flow-limitation • Flattening of inspiratory flow loop curve • Variable occurrence of symptoms during exercise-challenge Flexible laryngoscopy • Inspiratory adduction glottic or supra-glottic structures	Lung function • No abnormalities • Variable occurrence of symptoms during exercise-challenge Cardiopulmonary exercise testing • ↓ Arterial CO2 (only for hyperventilation)	Lung function • Abnormalities: restrictive, obstructive, mixed or normal pattern depending on the underlying cause	Lung function • No abnormalities at baseline Cardiopulmonary exercise testing (CPET) • No abnormal findings • Often lower VO2 max at peak exercise intensity
Treatment	SABA+ICS before or during exercise.	Patient information about benignity. Speech- and physiotherapy. Surgery only for severe structural causes.	Patient information about benignity. Speech- and physiotherapy	Treatment for cause of cough	Patient information about benignity. Encourage more exercise.

Abbreviations: DB: dysfunctional breathing EIB; exercise-induced bronchoconstriction, ENT; ear nose throat, VO2 max; Maximum volume of oxygen uptake,

4.7 Impact of EIS

Quality of life

Quality of life is reduced in children with asthma symptoms triggered by exercise compared with children who have asthma symptoms not triggered by exercise according to several studies. A Japanese study 35.000 school children used the ISAAC questionnaire to study asthma-related symptoms and the KINDL questionnaire to study quality of life (98). They found that children with asthma who reported wheeze during exercise have a lower quality of life score than children who reported asthma but no symptoms during exercise. A study in 160 adolescent athletes found a reduced health-related quality of life in adolescents with dyspnoea during exercise compared with no dyspnoea during exercise (99). Additionally, evidence suggest that quality of life in children with EIB is lower in females compared with males (100).

Physical activity

There is little evidence showing that children with asthma are less active than children without asthma (101), however evidence suggest that children with EIB are less active than children without EIB. A study in 607 schoolchildren aged 10-12 years showed that children with EIB were more often inactive than children without EIB (measured with exercise-challenge test) (37). In a Dutch study in 26 children aged 4-14 with asthma they found that children with EIB spent less time in moderate and vigorous activity than children with no EIB (102). While several studies have investigated the association between EIB and physical activity, little evidence exist on the relationship between physical activity and EIS of other causes than asthma (e.g. dysfunctional breathing). A study in 45 adults found that patients with dysfunctional breathing more often found that their breathing problems prevented them from being physically active than patients with asthma (103). A Swedish study in 1002 adolescents investigated the association between self-reported type of EIS and physical activity over a five-year period (104). They found that between the age of 12-13 and 17-18 years the prevalence of self-reported exercise-induced wheeze, cough, chest and throat tightness, hoarseness, and stridor increased while the number of days being physically active

decreased. Using logistic regression modelling, adjusted for sex, current asthma, weight, exercise-induced symptoms at baseline, and smoking at follow-up, they showed that adolescents who were more physically active at age 12-13 were more likely to report any (new onset) EIS at age 17-18 years. This indicates that children who are more active might be more likely to experience symptoms during exercise. What we don't know and what no studies have shown data on yet, is whether children who experience EIS are more likely to become less physically active to avoid provoking symptoms.

4.8 Summary

EIS are common in childhood and can have different causes. Identification of the correct diagnosis is important in order for appropriate management to prevent symptoms and thereby prevent possible long-term effects of EIS such as physical activity avoidance and decreased quality of life. Most commonly, EIS are caused by EIB but other common causes are extrathoracic and thoracic dysfunctional breathing, chronic cough, and insufficient fitness level. Reported symptoms and diagnostic investigations help to diagnose EIS. Different diagnoses share clinical presentations, diagnoses sometimes coexist, and objective diagnostic tests do not always provide conclusive results, which makes it difficult to identify the correct cause of EIS in children. Previous research has mainly focused on single diagnosis groups in children with EIS (e.g. EIB or ILO), and few studies have described the spectrum of diagnoses given to children with EIS. Symptoms in children with EIS have also mainly been described for single diagnoses, and few studies have compared symptoms between diagnosis groups. This PhD thesis provides novel epidemiological knowledge on diagnosis, diagnostic investigations, and reported symptoms in children with EIS and compare how clinical presentations differ between diagnosis groups.

5 Aims

5.1 Overall aims

In my PhD, I studied respiratory problems in childhood and focused especially on exercise-induced respiratory symptoms. Specifically, I aimed to

1. Build a clinical cohort of children referred for respiratory problems to paediatric outpatient clinics in Switzerland (Publication 1)
2. Study diagnosis, diagnostic investigations and management in children referred to paediatric outpatient clinics for exercise-induced respiratory symptoms (Publication 2)
3. Study symptoms in children with exercise-induced respiratory problems and analyse which symptoms are most useful to differentiate diagnoses of EIS (Publication 3)
4. Study exercise-induced symptoms recorded by physicians in the clinical history and study the agreement with exercise-induced symptoms reported by parents in a standardized questionnaire (Publication 4)
5. Validate a model to predict childhood asthma in children with symptoms at preschool age (Publication 5)

Only little evidence exist on which diagnoses are given to children seen for EIS, how they are diagnosed, and which symptoms they experience. With this research, I tried to shed light on these understudied problems.

5.2 Specific aims

Publication 1: The Swiss Paediatric Airway Cohort (SPAC)

Most evidence on respiratory problems in childhood comes from population-based studies or small clinical cohorts including relatively low numbers of symptomatic children. I together with colleagues therefore aimed to set up a clinical cohort of children and adolescents referred to paediatric outpatient clinics in Switzerland for recurrent wheeze, cough, dyspnoea, sleep- or exercise-related respiratory symptoms.

Publication 2: Diagnosis in children with exercise-induced respiratory symptoms – a multicentre study

Exercise-induced symptoms are common in childhood and have mostly been associated with exercise-induced bronchoconstriction, however other common causes include dysfunctional breathing, low fitness level, and chronic cough. No studies have reported the prevalence of different diagnoses and diagnostic practices in representative populations of children with EIS. I therefore studied diagnostic investigations, final diagnosis, and management in children referred to paediatric respiratory outpatient clinics for EIS and compared this to the diagnosis proposed by the referring physician.

Publication 3: Symptoms differentiate diagnoses in children with exercise-induced respiratory symptoms – findings from the Swiss Paediatric Airway Cohort (SPAC)

Diagnosis in children with EIS can be difficult to distinguish because different diagnoses share similar clinical presentations. There are however certain symptoms that are more associated with specific diagnoses than others. I therefore studied which parent reported symptoms are most useful to distinguish different diagnoses of EIS in children referred to paediatric respiratory outpatient clinics in Switzerland.

Publication 4: Exercise-induced symptoms reported by physicians

Reporting EIS when taking the clinical history is essential for arguing the most likely diagnosis and for assessing symptom control during follow-up care. I aimed to describe EIS reported by physicians in the clinical history and study if EIS were reported more often depending on final diagnosis. Secondly, I aimed to compare EIS reported by physicians in the clinical history with EIS reported by parents in a standardized questionnaire and assess agreement.

Publication 5: The simple 10-item predicting asthma risk in children tool to predict childhood asthma – an external validation

Several childhood asthma prediction models have been developed but few have been externally validated. External validation of prediction models is essential for assessing generalizability to other populations than the one it was developed in. The Predicting Asthma Risk in Children (PARC) tool was developed in the LRC to predict asthma in school age among children who had symptoms in preschool age. I aimed to externally validate the PARC tool using the ALSPAC study as external validation population.

6 Methods

The main publications of this PhD thesis cover the methodologies used for the single projects. In this chapter, I elaborate on aspects of the SPAC study that are not described in detail in the main publications including the development, management and recruitment status of the study.

6.1 Swiss Paediatric Airway Cohort (SPAC)

The initiation of SPAC

The SPAC study was conceptualized and planned by Claudia Kuehni in collaboration with paediatric pulmonologists from different children's hospitals in Switzerland. Claudia Kuehni submitted a grant proposal to the Swiss National Science Foundation (SNSF) in April 2015, which was granted in August 2015 covering funding for 3 years. I started to work on the project as a PhD student in April 2016. I first contributed with writing and submitting the application to the ethical committee in Bern. In January 2017, Carmen de Jong started as a second PhD student on the SPAC project. Together with Claudia Kuehni and the collaboartors, we finalized the study documents including patient information sheets, informed consent forms, and the baseline parental questionnaire. We created the study database using the REDCap system (105). During spring 2017, we held meetings in the first SPAC clinics to organize the recruitment procedures and to discuss management responsibilities with all involved persons (physicians, nurses, technicians, and administrative staff). The first SPAC study patients were recruited in July 2017.

Recruitment and management of SPAC

The recruitment procedures were adapted to each hospital to fit different systems for inviting and managing patient visits. Initially, we wanted all SPAC patients to receive the invitation to the study before their clinical visit including study information, consent forms and baseline questionnaire at home to fill in and bring to their appointment at the hospital. However, in some clinics, this recruitment model was not feasible and patients were instead invited directly when they arrived for their clinical appointment at the hospital. The parents

then filled in the baseline questionnaire at home and sent it directly to us at the Institute of Social and Preventive Medicine (ISPM).

From the start of the SPAC study until June, 2019, Carmen de Jong and I were responsible for the management of the study, the data collection, and the data entry into the REDCap database. The responsibilities for the SPAC clinics were divided: I managed the centres: Zurich, Lucerne, and Chur, and Carmen de Jong managed the centres: Worb, Bern, Basel, Aarau, and St. Gallen. In January 2018, Cristina Ardura-Garcia started as postdoc on the SPAC project. In June 2019 Christina Mallet started as a third PhD student on the SPAC project.

Recruitment status of SPAC by January 7, 2020

By January 7, 2020, the SPAC study is recruiting patients in 10 different clinics in Switzerland. The recruiting centres include two private pulmonology clinics in Worb and Horgen, and eight hospitals in Bern, Zurich, Lucerne, Basel, Aarau, St. Gallen, Chur and Lausanne. A total of 3113 patients were invited to SPAC of which 1893 agreed to participate in the study (61%) (**table 2, figure 3**). The response rate differed from 50-87% in the centres. Population characteristics are displayed by centre in **table 3**. Comparing the different centres, age at recruitment ranged from 7-11 years, with a proportion of girls from 34-47%. The range of the following environmental exposures differed between the centres at baseline: smoking mother 9-23%, smoking father 21-42%, and mould in the house 5-18%. Most children had lived in Switzerland since birth (range: 69-88%).

Table 2: Overview of SPAC recruitment by centre and in total

	Aarau	Basel	Bern	Chur	Horgen	Lucerne	StGallen	Worb	Zurich	Total
Months part.	18	25	28	16	2	29	18	30	30	30
Invited[1]	422	285	444	84	19	597	223	89	870	3113
Participated[2]	229	155	263	60	14	519	164	55	434	1893
- Quest. returned[3]	226	153	260	59	13	462	160	54	422	1809
- Consented[4]	211	127	237	59	13	517	163	53	394	1774
Refused[5]	14	8	22	1	1	76	3	7	32	164
No response[6]	229	122	159	23	4	2	56	27	404	1106
Response rate	54 %	54%	59%	71%	74%	87%	74%	62%	50%	61 %

Part. = participated, Quest. = questionnaire. [1]Number of patients invited (received documents by post or at the clinic); [2]Number of patients who returned informed consent form or returned a completed questionnaire; [3]Number of patients who returned a completed questionnaire; [4]Number of patients who returned a signed informed consent form (some patients have returned questionnaires but forgot to send back informed consent form); [5]Number of patients who refused to participate; [6]Number of patients from whom we have no response yet; [7]Proportion of participating patients of total invited patients. For Lausanne, 80 patients have been invited but none have been recruited yet as they are not recruited before coming for their clinical visit.

Figure 3: Number of participating patients per SPAC centre

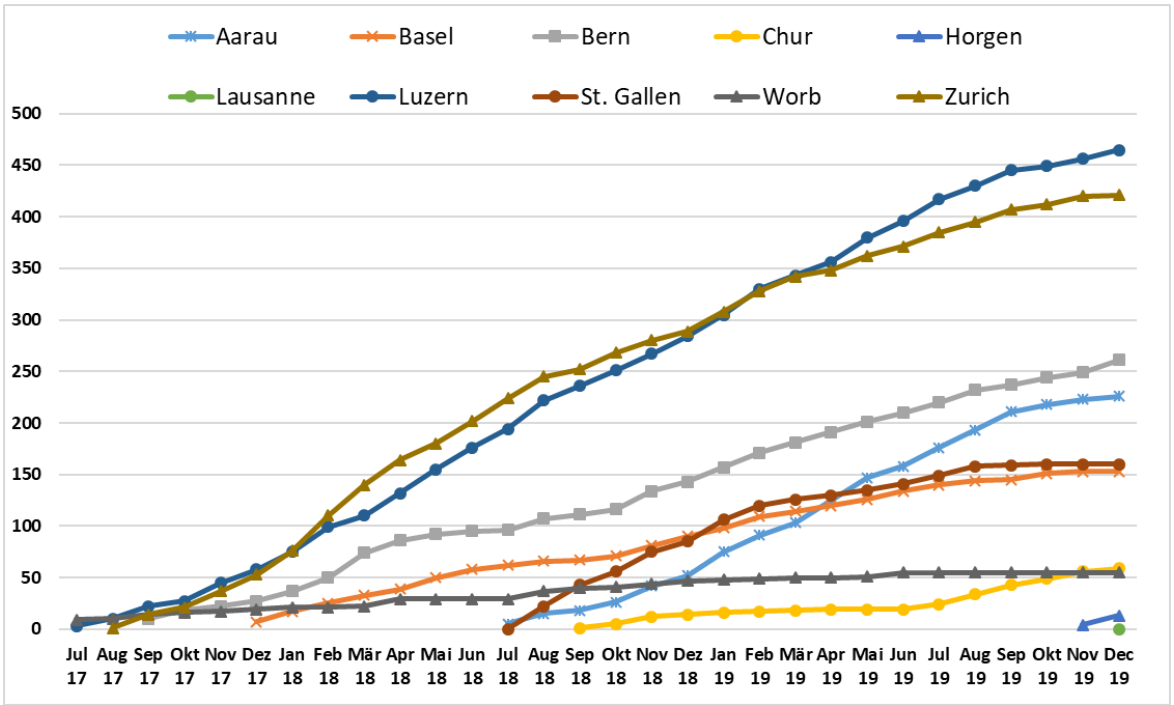


Table 3: Characteristics of SPAC population in centres with at least 20 participating children and a completed baseline questionnaire (N=1767)

	Lucerne	Zurich	Worb	Basel	Chur	Aarau	St. Gallen	Bern	Total
Characteristics	N=523	N=394	N=53	N=127	N=59	N=211	N=163	N=237	N= 1767
Demographics									
Age at recruitment, mean (SD) (n=1767)	7.7 (4.1)	9.6 (4.2)	8.5 (4.8)	9.5 (4.5)	6.9 (4.5)	9.2 (3.9)	11 (3.5)	7.4 (4.4)	8.7 (4.3)
Sex (girls) (n=1767)	202 (39)	144 (37)	19 (36)	60 (47)	20 (34)	79 (37)	65 (40)	92 (39)	681 (39)
Sports apart from school (n=1441)	258 (71)	256 (73)	23 (59)	75 (67)	30 (67)	131 (69)	112 (72)	123 (68)	1008 (70)
Environmental exposures									
Mother smokes (n=1642)	69 (16)	48 (13)	5 (9)	22 (18)	13 (23)	36 (18)	29 (19)	35 (15)	259 (16)
Father smokes (n=1594)	105 (25)	77 (21)	13 (25)	41 (34)	23 (42)	44 (22)	37 (24)	72 (31)	402 (26)
Mold in the house past 12 months (n=1589)	39 (9)	31 (9)	6 (12)	17 (14)	10 (18)	20 (10)	8 (5)	29 (13)	160 (10)
Origin									
Child lives in CH since birth (n=1638)	416 (95)	349 (92)	46 (88)	112 (91)	53 (93)	190 (94)	144 (92)	222 (96)	1532 (94)
Education									
Mother went to university (n=1611)	42 (8)	122 (31)	3 (6)	35 (28)	8 (14)	27 (13)	12 (7)	39 (16)	288 (18)
Father went to university (n=1592)	52 (12)	137 (37)	5 (10)	35 (30)	5 (9)	32 (16)	17 (11)	39 (17)	322 (20)
Respiratory symptoms									
Wheeze past 12 months (n=1638)	276 (63)	220 (58)	27 (52)	92 (74)	43 (74)	115 (57)	93 (59)	134 (58)	1000 (61)
>3 wheeze attacks past 12 months (n=1638)	144 (33)	96 (25)	9 (17)	57 (46)	17 (29)	50 (25)	35 (22)	61 (26)	469 (29)
Any exercise-induced symptoms, yes (n=1608)	250 (59)	252 (67)	32 (63)	84 (69)	32 (56)	108 (54)	98 (65)	126 (55)	982 (61)

7 Results: Main publications

7.1 Publication 1: The Swiss Paediatric Airway Cohort (SPAC)

Pedersen ESL*, de Jong CCM*, Ardura-Garcia C, Barben J, Casaulta C, Frey U, Jochmann A, Latzin P, Moeller A, Regamey N, Singer F, Spycher B, Sutter O, Goutaki M, Kuehni CE.

*Shared first-authorship

Original article (study protocol)

Published in European Respiratory Journal Open Research, 2018

Own contribution: Set up cohort study, implement recruitment procedures, data collection, draft manuscript, implement comments from co-authors, submit manuscript.

The Swiss Paediatric Airway Cohort (SPAC)

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ABSTRACT Chronic respiratory symptoms, such as cough, wheeze and dyspnoea, are common in children; however, most research has, with the exception of a few large-scale clinical cohort studies, been performed in the general population or in small, highly-selected samples.

The Swiss Paediatric Airway Cohort (SPAC) is a national, prospective clinical cohort of children and adolescents who visit physicians for recurrent conditions, such as wheeze and cough, and exercise-related respiratory problems. The SPAC is an observational study and baseline assessment includes standardised questionnaires for families and data extracted from hospital records, including results of clinically indicated investigations, diagnoses and treatments. Outcomes are assessed through annual questionnaires, monthly symptom reporting *via* mobile phone and follow-up visits.

The SPAC will address important questions about clinical phenotypes, diagnosis, treatment, and the short- and long-term prognosis of common respiratory problems in children. The cohort currently consists of 347 patients from four major hospitals (Bern, Zurich, Basel and Lucerne), with 70–80 additional patients joining each month. More centres will join and the target sample size is a minimum of 3000 patients.

The SPAC will provide real-life data on children visiting the Swiss healthcare system for common respiratory problems and will provide a research platform for health services research and nested clinical and translational studies.

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The Swiss Paediatric Airway Cohort (SPAC) is a unique research platform for common respiratory problems in children http://ow.ly/Y1v030lDnji

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Introduction

Many children suffer during their childhood from repeated episodes of wheeze, cough, or dyspnoea [1–4]. These symptoms are typical for childhood asthma, but are also seen in other diseases. Childhood asthma is characterised by a range of phenotypes that might reflect distinct aetiologies [5–9]. Symptoms vary over time, with short-term diurnal and seasonal fluctuations and a variable long-term course. Factors determining clinical course are poorly understood and the available prediction tools have limited accuracy [10]. In addition, the diagnosis of asthma is not straightforward and making the distinction from healthy children and children with other underlying problems can be difficult [11, 12].

Another common and possibly related respiratory problem in childhood is recurrent or chronic cough (without wheeze), which affects up to 20% of preschool and schoolchildren [3, 13–15]. Chronic cough is a key symptom of asthma and upper respiratory tract allergies, but also occurs as prolonged post-infectious cough after viral or atypical bacterial infections, as psychogenic or habit cough, with a retained foreign body, with gastro-oesophageal reflux, or with persistent bacterial bronchitis. Rarely, it reflects a serious underlying condition such as a lung malformation, cystic fibrosis (CF), primary ciliary dyskinesia or immunodeficiency [16]. Finally, exercise-induced respiratory problems are frequent in children with asthma, but can have other causes such as vocal cord dysfunction, laryngomalacia, or primary hyperventilation [17].

Many studies have investigated the epidemiology of childhood asthma. Most were conducted in the general population, such as the International Study on Asthma and Allergies in Childhood (ISAAC) [18, 19], or in birth cohorts [20–24]. Population-based studies are useful for investigating asthma incidence; however, as most children in birth cohorts are healthy or have mild disease, they are of limited utility for studying phenotypes and long-term course. As such, even large cohorts have limited statistical power for studying long-term outcomes of clinically relevant disease. In addition, population-based studies typically rely on questionnaires and simple measurements such as spirometry and allergy tests.

Several clinical cohorts of children with asthma have been established [25–28]. However, their inclusion criteria emphasise asthma alone (*e.g.* requiring a diagnosis of suspicion of asthma) and do not fully represent the broad mix of phenotypes seen in healthcare. To our knowledge, no multicentre cohort studies have focused on children with recurrent cough as the sole symptom and children with exercise-related symptoms.

Although abundant diagnostic and clinical data are routinely collected by the healthcare system these are rarely used for research. They are of limited value if collected retrospectively from patient records, but can be very valuable if collected prospectively in a standardised way. The Swiss Paediatric Airway Cohort (SPAC) was set up in 2017 as a large, longitudinal database representative of children and adolescents visiting physicians in Switzerland for recurrent wheeze and cough, and exercise-related respiratory symptoms. The SPAC will constitute a national research platform for studying healthcare provision, phenotypes and prognosis, and a sampling frame for conducting nested studies. This article explains the SPAC's aims and its methods, and outlines how the data can be accessed for future research.

Study objectives

The SPAC is a multipurpose cohort study of children seeking medical care for common lower respiratory problems (cough, wheeze and dyspnoea). Its objectives are: 1) to describe the spectrum and relative frequency of respiratory problems in children visiting pulmonary outpatient clinics and paediatric practices in Switzerland; 2) to distinguish clinical phenotypes of wheeze and cough, and describe associations with physiological traits and measurements; 3) to investigate long-term trajectories and their determinants, and to develop and improve clinical prediction tools; 4) to document diagnostic practises, treatment strategies and preventive measures used in healthcare in Switzerland; 5) to act as a sampling frame for identifying and recruiting children for specific nested studies.

Methods

Study design

The SPAC is a national multicentre observational study which is integrated into the routine care given by hospitals and practices. Patients are managed according to local procedures and policies with no interference from the study team. No examinations are performed specifically for the SPAC and baseline information is collected prospectively when patients visit the clinic for the first time. Follow-up data are collected by different means, including: medical data from follow-up appointments, questionnaires sent yearly to the families (parents or children themselves from the age of 16 years) and monthly symptom scores assessed *via* a responsive web application. The study has no specified endpoint, is hosted at the Institute of Social and Preventive Medicine (ISPM, hereafter called the SPAC data centre) at the University of Bern, Switzerland and is managed in close collaboration with all participating SPAC clinics.

Study population

Inclusion criteria and participating centres

Patients are included in the SPAC if they are referred to a paediatric respiratory outpatient clinic (or visit a primary care physician repeatedly) for lower respiratory problems such as wheeze, cough, or dyspnoea, or exercise-related breathing problems. This includes children with concomitant upper respiratory symptoms such as sinusitis, rhinitis or adenoid hyperplasia. Eligible patients must be below 17 years old, resident in Switzerland and able to speak sufficient German or French to answer the questionnaire. Exercise-related breathing problems can be wheeze, cough, chest tightness or dyspnoea triggered by exercise.

Excluded children are those with a prior diagnosis of a severe lung disease, such as CF, primary ciliary dyskinesia, severe heart disease, oncological disease, neuromuscular disease, or severe disability (diseases for which there are specific registries) [29]. The SPAC also excludes children who are referred specifically to perform sleep studies for evaluation of sleep-disordered breathing. Exclusion criteria are deliberately few in order to allow the recruitment of a study population representative of the entire spectrum of common lower respiratory problems in childhood, including pre-school viral wheeze, chronic cough and exercise-related problems.

In the first phase, we aim to recruit children from outpatient clinics at all of the major paediatric hospitals in Switzerland (Basel, Bern, Zurich, Lucerne, St. Gallen, Aarau, Lausanne and Geneva). At a later stage, we will open the study to smaller hospitals and paediatric practices.

Study procedures

Patient identification and recruitment

Set in different clinics and practices, SPAC logistics vary slightly between centres because systems for planning, inviting and organising patient visits differ (figure 1). Families receive a SPAC information package containing an invitation letter, study information leaflet, informed consent form and questionnaire either in the letter that invites them to the clinic, or upon arrival at the hospital. In both cases, physicians introduce the study to them, answer questions and collect informed consent forms. Families return the completed questionnaire sent to them ahead of time during their visit to the clinic. In the case where clinics distribute the questionnaire upon arrival, families send it directly to the SPAC study centre using a prepaid return envelope. Families who consent but fail to return the questionnaire are mailed a reminder letter with another questionnaire and a prepaid return envelope after 4 weeks. If families do not respond to the first reminder letter, they receive a second reminder 2 months after the first reminder.

Clinical assessments and collection of data from hospital records

No tests are performed specifically for the SPAC and examinations such as lung function, allergy, blood and bronchial challenge tests are performed only if clinically indicated or if requested by the referring physician (using the respective standard procedures in the clinics involved). The SPAC research team members visit participating centres at regular intervals. Relevant data are extracted from paper and electronic hospital records and entered into the SPAC database.

Follow-up data

One year after enrolment in the SPAC, caregivers or patients who are 16 years of age or older will receive a follow-up questionnaire by email, text message (sms), or post (figure 2). This will be repeated yearly. Nonresponders will receive a second copy of the follow-up questionnaire after 4–6 weeks and those who do not respond to the second mailing will be contacted by phone. Provided sufficient funding is available, we will also collect medical data from follow-up visits. Beginning in 2019, we will ask for short monthly updates on symptoms, treatments and healthcare utilisation using a simple smart phone app. This will provide prospective data on respiratory symptoms during the year following the baseline medical visit.

What information is collected

Information from questionnaires

At baseline, families complete a detailed questionnaire that includes sections on frequency, duration, severity, triggers and history of upper and lower respiratory symptoms, as well as diagnoses, treatments, health behaviours, environmental factors, family history and contact information (table 1).

The follow-up questionnaires are shorter and focus on symptoms, treatments and important risk factors during the past 12 months (table 1). Postal addresses for mailing are obtained from hospital records and updated by contacting community registration offices, a procedure used successfully for other registries and cohort studies in Switzerland [30]. Questionnaires are currently available in German, but will be translated into French.

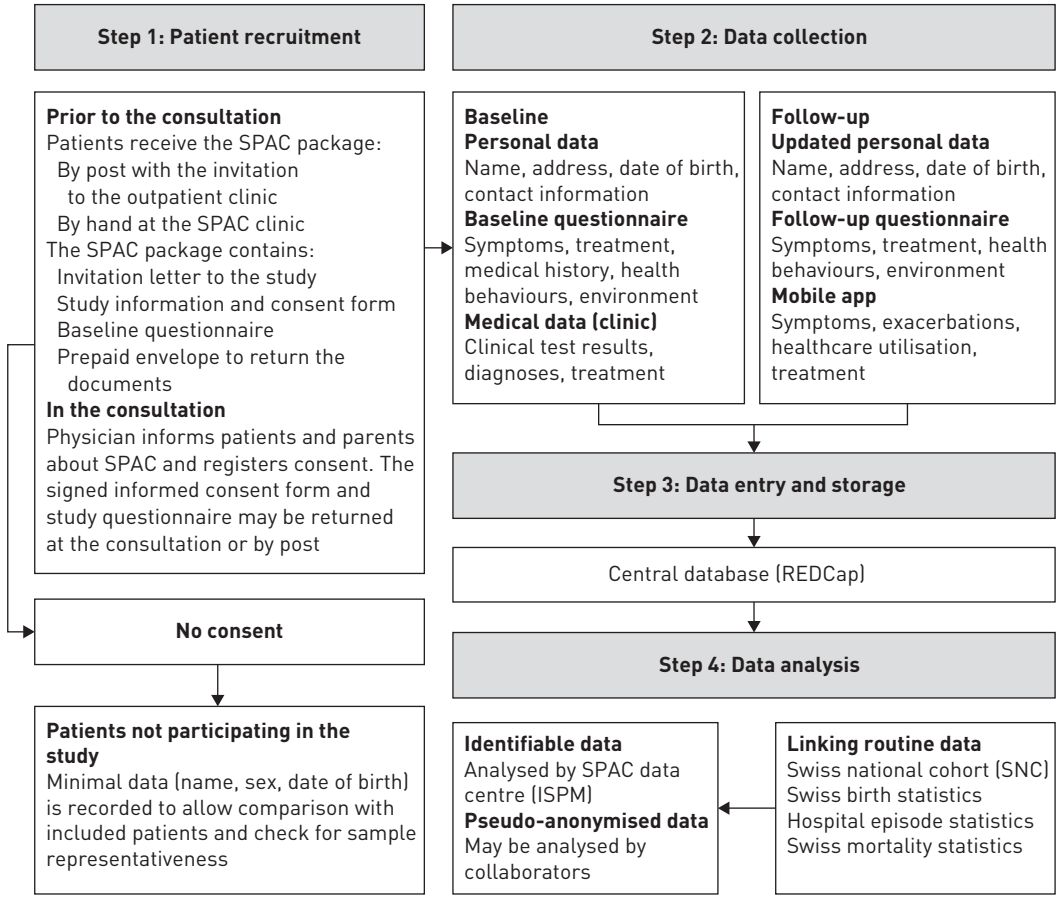

FIGURE 1 Schematic chart of data collected in the Swiss Paediatric Airway Cohort (SPAC). REDCap: Research Electronic Data Capture (www.project-redcap.org); ISPM: Institute of Social and Preventive Medicine.

Information from medical records

Information obtained from medical records includes reasons for referral, anthropometric measures, results from physical examinations and diagnostic tests (including pulmonary function tests (PFTs), allergy tests and blood tests), final diagnoses and prescribed treatments (table 1).

Information from the mobile app

From 2019 onwards, parents of participating children and children aged 12 years or older will complete a short questionnaire on symptoms, exacerbations, emergency visits, hospitalisations and use of medication through a simple mobile app. This app will be an adapted version of an existing app called "e-symptoms", developed jointly by the Allergiezentrum Schweiz (www.aha.ch) and CK-Care (www.ck-care.ch) foundations.

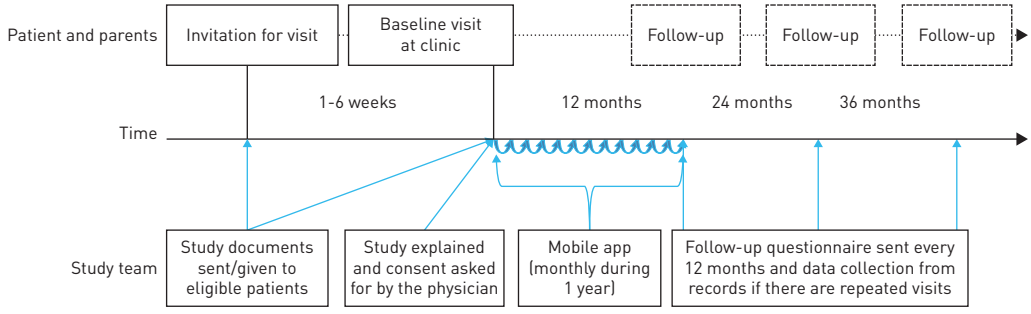

FIGURE 2 Timeline and follow-up procedures of the Swiss Paediatric Airway Cohort.

TABLE 1 Description of data collected for the Swiss Paediatric Airway Cohort (SPAC)

Source	Baseline	Follow-up
Questionnaire data		
Reason for referral	X	
Colds and coughing (frequency, duration, history, severity and triggers)	X	X
Wheeze (frequency, duration, history, severity and triggers)	X	X
Exercise-related breathing problems (frequency, duration, history, severity and triggers)	X	X
Ear, nose and throat (frequency, duration, history and severity of specific conditions, *e.g.* rhinitis, hay fever and otitis)	X	X
Sleeping problems (frequency, duration, history and severity of specific conditions, *e.g.* sleep apnoea)	X	X
Skin (frequency, duration, history, severity and location of specific conditions, *e.g.* eczema)	X	X
Diagnosis and treatment (number of visits to the GP or paediatrician, causes for visiting a physician, tests performed, medication taken (inhaler medication, oral medication, nasal sprays, eye drops and antibiotics), other chronic illnesses, alternative treatments and vaccinations)	X	X
Lifestyle and environment (physical activity, sedentary behaviour, smoking, pets, living on a farm, mould in the house and humidifier use)	X	X
Origin and family (citizenship, siblings, parental education and profession, family history of asthma, hay fever and eczema)	X	
Perinatal factors (pregnancy complications, gestational age, birth weight and length, and breastfeeding)	X	
Contact information (address, telephone number and email address)	X	X
Data from medical records		
Personal information (date of birth, sex, referring physician and responsible primary care physician)	X	
Disease (diagnoses, dates and results of diagnostic testing, and prescribed treatments)	X	
Measurements[#] (weight, height, PFTs (*e.g.* spirometry and plethysmography), F_{ENO}, spiroergonometry or other exercise challenge tests, bronchial challenge tests (*e.g.* mannitol and methacholine), allergy tests (total IgE, RAST and SPT), laboratory tests (blood cell count, inflammatory markers and blood gas analysis), imaging (radiography, CT scan and MRI), microbiology (BAL, sputum and smear), oxygen saturation and P_{tcO_2}, bronchoscopy, and special examinations used for differential diagnosis (*e.g.* chloride sweat test))	X	
Mobile app data		
Symptoms (ear, nose, throat, cough, dyspnoea and wheezing)		X
Exacerbations (acute worsening of respiratory symptoms)		X
Healthcare utilisation (hospitalisations and emergency care visits)		X
Treatment (respiratory symptoms medication)		X
Routine data and linkage		
SNC (environmental exposures (for special analyses) and socioeconomic measures (maternal and paternal education and profession, number of rooms and persons per household, square meter living space per person and area-based socioeconomic position index))	X	
Swiss birth statistics[¶] (gestational age, birth weight and height, and head circumference)	X	
Hospital episode statistics[¶] (type of hospital, length of stay, type of discharge, referral pathways, diagnosis and treatments (ICD-10, procedure and DRGs))		X
Swiss mortality statistics[¶] (date and cause of death (ICD-10), age, sex, profession, place of residence and citizenship)		X

GP: general practitioner; PFT: pulmonary function test; F_{ENO}: exhaled nitric oxide fraction; RAST: radio allergo sorbent test; SPT: skin prick test; CT computed tomography; MRI: magnetic resonance imaging; BAL: bronchoalveolar lavage; P_{tcO_2}: transcutaneous oxygen tension; SNC: Swiss National Cohort; ICD-10: international classification of diseases-10th revision; DRG: diagnosis related group. [#]: only if measurements are taken for clinical reasons; [¶]: birth, hospital episode and mortality statistics will be obtained from the Swiss Federal Statistical Office.

Linkage to routine data

For specific analyses, we will use probabilistic record linkage to merge data from the SPAC with routine datasets collected by the Swiss Federal Statistical Office, as was done for the Swiss Childhood Cancer Registry (SCCR) [31–33]. This includes information on birth and mortality statistics, national censuses and hospital episode statistics. These data have been linked to build the Swiss National Cohort (SNC), a longitudinal research platform including the entire population of Switzerland [34]. This allows perinatal data, causes of hospitalisations and deaths, socioeconomic indicators and spatially distributed environmental exposures (such as traffic-related air pollution) to be obtained.

Study database

The SPAC database is web-based, using the Research Electronic Data Capture (REDCap) platform developed at Vanderbilt University (www.project-redcap.org). REDCap is widely used in academic research and allows data entry and extraction in various formats. The REDCap environment is completely secure and only a limited number of research staff from the SPAC research team will have access to the whole dataset. Furthermore, principle investigators at the participating clinics will have access to data from

only their own clinic. Data entered through the mobile app will be automatically forwarded *via* a secure connection to a central, secure database accessible only by the study team.

Ethics and data protection

Ethical approval for the study was obtained from the Bern Cantonal Ethics Committee (Kantonale Ethikkommission Bern 2016-02176). Written informed consent to participate in the study is obtained from patients' parents or directly from patients of 14 years of age or older. Patients can withdraw their consent and their data from the SPAC study at any time by contacting the SPAC clinic or the SPAC data centre. Data generation, transmission and storage, as well as analysis of health-related personal data within the SPAC study, follow the current Swiss legal requirements for data protection. Employees are trained in data protection and must sign an agreement for dealing with particularly sensitive data.

Study power and sample size

We plan to recruit at least 3000 patients for the SPAC. This number is based on project feasibility and the annual number of patients seen in the paediatric respiratory outpatient clinics in Switzerland. For children with asthma (an estimated 60–70% of the cohort) this number will allow us to perform analyses such as latent class analyses that involve models with numerous parameters. For developing prognostic models, 10 events are required for each predictor variable entered into the model. A large sample size is also needed to study rarer outcomes such as chronic cough, vocal cord dysfunction and emergency hospital admissions. After reaching 3000 patients, recruitment will continue on a reduced scale, focusing on specific diagnostic subgroups or patients of higher severity.

How data can be accessed

Participating centres have continual access to their own datasets and can export them directly in various formats for local analyses. The study of SPAC data from several centres is regulated by the SPAC committee, which consists of the SPAC clinics and members of the SPAC data centre. Researchers who wish to use data should submit a concept sheet describing the planned analysis to the SPAC committee for approval (see supplementary material). If the SPAC Committee agrees, a publication agreement (see supplementary material) is signed and the SPAC data centre prepares a partial dataset for the proposed analysis. The SPAC data centre will work closely with and support the lead researchers of each study. Researchers who wish to develop a nested study with inclusion of additional data also need to submit a proposal to the SPAC committee and request permission. Additional data collected by nested studies must be contributed to the SPAC database after the study. Nested studies might also need separate ethics permission.

Current status and initial results

The first clinics (Lucerne, Bern, Zurich and Basel) began recruiting patients in 2017. During the first months, procedures were revised to fit the requirements of each centre. Currently, 60–80 new patients enter the SPAC every month and enrolment is accelerating (figure 3). St. Gallen and Aarau plan to join in 2018, Lausanne and Geneva in 2019.

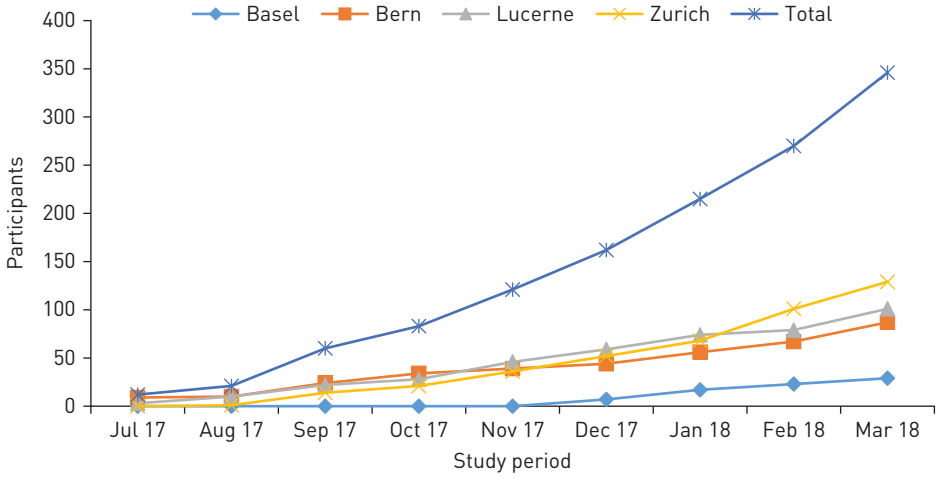

FIGURE 3 Number of participants in the Swiss Paediatric Airway Cohort, from study start in July 2017 to March 2018.

Until March 2018, 347 out of 851 eligible patients (41%) consented and returned the baseline questionnaire (table 2). In addition, there were 16 eligible patients who consented but have yet to return the baseline questionnaire. Participation rates varied significantly between hospitals and were 88%, 64%, 33% and 29%, respectively, in the four centres (Lucerne, Bern, Zurich and Basel), with lower response rates in larger hospitals. Of the patients who participated, 29% were aged less than 5 years, 33% were aged 5–9 years and 38% were aged 10–15 years. Sixty-two percent were males. During the past 12 months, 64% had wheezed, 50% had night cough apart from colds, 60% had exercise-induced symptoms and 13% had habitual snoring (on most nights). In older children, wheeze and night cough were less common than in younger ones, while exercise-induced symptoms were more common. About 19% of mothers and 28% of fathers smoked, 4% of children lived on a farm and 34% kept pets at home. During the past 12 months, 75% had used a short-acting bronchodilator and 56% had used an inhaled corticosteroid (ICS).

Discussion

The nationwide and multicentre SPAC is a clinical cohort of children visiting physicians for recurrent wheeze, cough, dyspnoea and exercise-induced respiratory problems. Patients are currently recruited from outpatient clinics of major paediatric hospitals, but smaller hospitals and primary care practices will be invited to join so that the SPAC will include the full spectrum of patients with common respiratory problems in Switzerland. The key features of the SPAC are shown in text box 1.

Only a few comparable clinical cohorts have been set up in other countries. One is the All Age Asthma Cohort (ALLIANCE), a national cohort of paediatric and adult patients with asthma in Germany, led by the German Centre for Lung Research (DZL) and registered at https://clinicaltrials.gov with identifier NCT02496468. ALLIANCE aims to identify biomarkers and predictors of different wheeze phenotypes and their longitudinal course. It differs in several aspects from the SPAC in that it recruits patients with a doctor's diagnosis of asthma and healthy controls, and performs an extensive set of measurements in all

TABLE 2 Characteristics of participants in the Swiss Paediatric Airway Cohort (SPAC) by March 2018

Characteristics	Total participants (n=347)	Participants by age		
		<5 years (n=99)	5–9 years (n=116)	⩾10 years (n=132)
Study centre				
Bern	87 (25)	27 (27)	26 (22)	34 (26)
Zurich	129 (38)	31 (31)	41 (35)	57 (43)
Lucerne	102 (29)	35 (35)	41 (35)	26 (20)
Basel	29 (8)	6 (6)	8 (7)	15 (11)
Demographics				
Age years	8±4	3±1	7±1	13±2
Male sex	214 (62)	67 (68)	68 (59)	79 (60)
Symptoms [#,¶]				
Wheeze	217 (63)	77 (78)	76 (66)	64 (48)
Cough at night apart from colds	167 (48)	48 (48)	61 (53)	58 (44)
Rhinitis apart from colds	188 (54)	43 (43)	67 (58)	78 (59)
Exercise-induced respiratory symptoms	200 (58)	36 (36)	63 (54)	101 (77)
Habitual snoring (most nights) apart from colds	46 (13)	10 (10)	15 (13)	21 (16)
Environmental exposures [¶]				
Maternal smoking	64 (18)	19 (19)	18 (16)	27 (20)
Paternal smoking	93 (27)	29 (29)	26 (22)	38 (29)
Living on a farm	15 (4)	6 (6)	3 (3)	6 (5)
Pets at home	118 (34)	22 (22)	38 (33)	58 (44)
Mould in the house	34 (10)	15 (15)	11 (9)	8 (6)
Physical activity				
Not very active	31 (9)	3 (3)	7 (6)	21 (16)
Moderately active	223 (64)	58 (59)	74 (64)	91 (69)
Very active	93 (27)	38 (38)	35 (30)	20 (15)
Treatment history [¶]				
Used inhaled SABA	259 (75)	82 (83)	95 (82)	82 (83)
Used ICS	184 (59)	55 (63)	59 (57)	70 (58)

Data is displayed as n (%) or mean±SD. SABA: short-acting β-agonists; ICS: inhaled corticosteroids; ISAAC: International Study of Asthma and Allergies in Childhood. [#]: questions on symptoms were based on questions used in the ISAAC study, either alone or in combination (*e.g.* pulmicort, axotide, seretide and symbicort); [¶]: data as recorded over the past 12 months.

Text Box 1 Key features of the Swiss Paediatric Airway Cohort (SPAC)

- National representative cohort study of children seen in respiratory outpatient clinics.
- Observational study embedded in routine care.
- Focus is on common respiratory problems in childhood (wheeze, cough, exercise- and sleep-related breathing problems).
- Combines patient reported symptoms with data from hospital records.
- Follow-up is *via* questionnaires and mobile app to families, and linkage to routine data.
- Research platform for nested studies.

children, including single and multiple breath wash-out tests and biomaterial collection (blood, swabs, stool and induced sputum samples) for "omics" studies. Two cohorts from the Netherlands studied preschool children seen in general practice for cough or suspected asthma. One was set up between 1995–1997 [27] and one between 2004–2006 (the ARCADE cohort) [28]. Both followed the children until the age of 6 years and, as in ALLIANCE, these cohorts focused on asthma. They were regional, not nationwide, recruiting participants only from primary care. The Childhood Asthma Management Programme (CAMP) started as a randomised controlled trial (RCT) of over 1000 children aged 5–12 years with asthma who were randomised to receive treatment with budesonide, nedocromil, or a placebo in eight clinical centres in the US and Canada [25, 26]. Follow-up was extended after the randomisation to study long-term outcomes. As for the other studies mentioned, inclusion criteria were narrow requiring mild to moderate asthma. A strength of this study is that all children received a full set of diagnostic tests and repeated clinical follow-up assessments, including multiple lung function tests.

The SPAC contrasts with all these studies because it is a real-life picture of a representative sample of all children visiting physicians for recurrent wheeze, cough, dyspnoea and exercise problems. Thus it does not only include children with typical doctor-diagnosed asthma, but the entire range of children with less typical features, whose diagnosis is often a challenge for paediatricians and pulmonologists. This setting (consecutive referrals) allows us to assess the value of screening tests, which is not possible in a case-control setting. The SPAC includes not only asthma, but also has a focus on chronic cough and exercise-induced dyspnoea of different aetiologies, both of which are under-researched entities. Being multicentre and observational, the SPAC includes a large proportion of the children referred for evaluation of respiratory disease in Switzerland and allows us to monitor healthcare practise (diagnostics and management) by both referring primary care physicians and hospitals.

This design also leads to weaknesses. First, although inclusion criteria are comprehensive, the study population is not totally representative. Recent immigrants, who do not speak French or German, are not eligible for the study. In addition, the response rate varied between hospitals from 29% to 88%, suggesting that in some clinics participants are not fully representative of all patients. Furthermore, not all hospitals currently participate and patients seen only in primary care are not currently part of the SPAC. However, despite these limitations, the SPAC represents the mix of patients seen in Switzerland better than a RCT would do, or a prospective study with a fixed set of measurements. Secondly, results from some measurements, such as bronchial challenge tests, will only be available for some patients, and the order and procedures for clinical examinations vary between hospitals. For example, hospitals use different protocols to perform exercise challenge tests. We intend to harmonise these procedures in the future where possible, but the SPAC will remain a real-life observational study. This variation might improve over time because the SPAC provides an opportunity for collaborating centres to harmonise their examinations and the ongoing harmonisation process of the Swiss Personalised Health Network will lead eventually to a more uniform set of data being collected in Swiss hospitals. Thirdly, the lack of sophisticated lung function tests, immunological examinations and biosamples limits the ability of the SPAC to perform deep endophenotyping. Some of these aspects will, however, be covered in nested studies.

In summary, the SPAC will provide a unique resource for studying the pathophysiology, clinical phenotypes and long-term course of common respiratory problems in children, as well as for assessing and comparing aspects of healthcare across Switzerland. This will make it an important research platform for clinical and translational studies on common respiratory problems in children.

Acknowledgements: The paper is presented on behalf of the SPAC study group. We thank all the members of each recruiting centre for their dedicated effort, devotion, promptness and care in the recruitment and assessment of the participants in this study.

Author contributions: C.E. Kuehni, B.D. Spycher, M. Goutaki and the SPAC study group developed the concept and designed the study. C.C.M. De Jong, E.S.L. Pedersen, A. Jochmann, A. Moeller, P. Latzin, C. Casaulta, F. Singer and

N. Regamey collected the data. C.E. Kuehni, E.S.L. Pedersen, C.C.M. de Jong, C. Ardura-Garcia and M. Goutaki drafted the manuscript. All authors contributed to iterations and approved the final version. C.E. Kuehni takes final responsibility for the contents.

Members of the SPAC study group (www.spac-study.ch): C. Barazzone-Argiroffo, University Children's Hospital, Geneva; J. Barben, Children's Hospital, St Gallen; C. Casaulta, University Children's Hospital, Bern; U. Frey, University Children's Hospital, Basel; A. Jochmann, University Children's Hospital, Basel; P. Latzin, University Children's Hospital, Bern; A. Moeller, University Children's Hospital, Zurich; N. Regamey, Children's Hospital, Lucerne; F. Singer, University Children's Hospital, Zurich; B.D. Spycher, University of Bern; O. Suter, Paediatric Primary Care, Worb; I. Rochat, University Children's Hospital, Lausanne; and C.E. Kuehni, University of Bern.

Conflict of interest: P. Latzin reports receiving personal fees from Gilead, Novartis, Roche, Schwabe, Vertex, Vifor and Zambon outside the submitted work.

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Supplementary document 1 - Template of a concept sheet for publications

Swiss Paediatric Airway Cohort

Concept sheet for publications

Title of project/abstract

- (first author)
- (last & corresponding author)

Co-authors:
- Writing Team
- Potential data providers

Data manager and statistician:
Short description of potential dataset:

Background:

Aims:

Methods:

- Inclusion criteria:
  - Clinics
  - Patients

- Variables that will be used:
  - Patient identifiers
  - Outcomes
  - Exposures
  - Additional variables

- Analysis plan:

Anticipated display items:

Funding:

Target journal(s):

Milestones:

References:

Supplementary document 2: Template for Publication Agreement

PUBLICATION AGREEMENT

between

University of Bern
Institute of Social and Preventive Medicine,
3012 Bern, Switzerland

(hereinafter referred to as "University")

And

_____

(hereinafter referred to as "Partner" or in the event of several partners as "Partners", as the case may be)

Preamble

WHEREAS, University and Partner participate in the SNSF funded research project "Swiss Paediatric Airway Cohort" ("Project"). During the Project, data from several sources are collected by the University and the Partners, and entered in a joint dataset that can be used for analysis and publications.

WHEREAS, University and Partner(s) have concluded a Data Transfer Agreement on _____ [execution date] and Partner has provided data to University for inclusion to the Project ("Data");

WHEREAS, the University and Partner intend to publish certain findings based on the Data.

The parties thus agree as follows:

Article 1: Publication

1.1 The parties intend to jointly publish, based on a concept sheet and an analysis dataset provided by University, the following scientific findings _____ [working title] in _____[Journal] ("Publication"). If the manuscript is rejected by the journal of choice, the choice of alternative journals will be made in discussion between University and all Partners.

1.2 As agreed in the Data Transfer Agreement, the following publication rules in accordance with the regulations of the International Committee of Medical Journal Editors shall apply:

- general authorship rules of the International Committee of Medical Journal Editors will be adhered to
- the first and last author will usually be from the institution which is responsible for the specific paper

- whenever possible, all partners contributing data will be offered a co-authorship.
- second and second last co-authorship will be offered to co-authors who have a major input in data analysis or writing, or who provided data on a very large number of subjects
- remaining co-authors will be listed alphabetically

Thus, the parties now agree upon the following authorship for publication:

- First author: _____
- Last author: _____
- Second author: _____
- Second last author: _____
- Co-authors or contributing partners defined according to the criteria of the International Committee of Medical Journal Editors; from University and from Partner(s):

_____

...

1.2 The planned timeline of the publication is as follows:

- results (tables) circulated by the responsible partner to all co-authors and data providers: _____
- first draft of the publication circulated by the responsible partner to all co-authors and data providers: _____
- final draft of the publication circulated by the responsible partner to all co-authors and data providers: _____
- latest possible date for submission of the publication to the target journal:

_____

1.3 If these deadlines are not kept and the manuscript is not submitted to the target journal 2 years after this Publication Agreement has been signed at the very latest, the responsible partner looses its leadership and the topic is again open for other data providers (upon circulation and acceptance of a concept sheet).

Article 2: Miscellaneous

No agreements altering or supplementing the terms may be made except by a written document signed by the duly authorized representatives of the parties.

For University:	**For Partner:**
Bern, Date: _____	Place, Date: _____
_____	_____
Prof. Dr. Claudia Kuehni Principal Investigator	_____ Collaborator

7.2 Publication 2: Diagnosis in children with exercise-induced respiratory symptoms: a multi-centre study

Pedersen ESL, Ardura-Garcia C, de Jong CCM, Jochmann A, Moeller A, Mueller-Suter D, Regamey N, Singer F, Goutaki M, Kuehni CE.

Original article

Under review at Archives of Disease in Childhood

Own contribution: Conceptualise and design study, prepare and analyse data, interpret results, draft manuscript and display items.

Archives of
Disease in Childhood

Diagnosis in children with exercise-induced respiratory symptoms: a multi-centre study

Journal:	*Archives of Disease in Childhood*
Manuscript ID	archdischild-2020-318819
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Diagnosis in children with exercise-induced respiratory symptoms: a multi-centre study

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Mandatory statements for Archives of Disease in Childhood

What is already known on this topic (2-3 statements of max 25 words)

1. Exercise-induced symptoms are common in childhood but not easy to diagnose because different diagnoses share similar clinical presentations
2. Only few studies focused on children with exercise-induced symptoms and all have included selected groups of patients with difficult-to-diagnose problems

What this study adds (2-3 statements of max 25 words)

1. Exercise-induced respiratory symptoms was the main reason for referral in one fifth of the children referred to paediatric respiratory outpatient clinics.
2. Dysfunctional breathing is an under-recognised diagnosis; it was frequently diagnosed in the outpatient clinic (in 37%) but rarely suspected by the referring physician (6%)
3. Diagnostic evaluation, management, and follow-up were inconsistent between clinics highlighting the need for diagnostic guidelines in children seen for EIS.

Abstract (248/250 words)

Objective: Exercise-induced respiratory symptoms (EIS) are common in childhood and reflect different diseases that can be difficult to diagnose. In children referred to respiratory outpatient clinics for EIS, we compared the diagnosis proposed by the referring primary care physician with the final diagnosis from the outpatient clinic and described diagnostic tests performed and treatment prescribed after the diagnostic evaluation.

Design: Observational study nested in the Swiss Paediatric Airway Cohort (SPAC), which includes respiratory outpatients aged 0-16 years.

Patients: We included children with EIS as main reason for referral. Information about diagnostic investigations, final diagnosis, and treatment prescribed came from outpatient records.

Results: 214 were referred for EIS (mean age 12 years, 99 (46%) female). The final diagnosis was asthma in 115 (54%), extrathoracic dysfunctional breathing (DB) in 35 (16%), thoracic DB in 22 (10%), asthma plus DB in 23 (11%), insufficient fitness in 10 (5%), chronic cough in 6 (3%), and other diagnoses in 3 (1%). Final diagnosis differed from referral diagnosis in 115 (54%). Spirometry, body plethysmography and measurements of exhaled nitric oxide were performed in almost all; exercise-challenge tests in a third. 91% of the children with a final diagnosis of asthma were prescribed inhaled medication and 50% of children with DB were referred to physiotherapy.

Conclusions: Diagnosis given at the outpatient clinic often differed from the diagnosis suspected by the referring physician. Diagnostic evaluation, management and follow-up were inconsistent between clinics and diagnostic groups, highlighting the need for diagnostic guidelines in children seen for EIS.

Introduction

Exercise-induced respiratory symptoms (EIS) are common in childhood,(1-3) but are not easy to diagnose because different aetiologies share similar clinical presentations.(4-6) EIS are typically due to asthma or exercise-induced bronchoconstriction, but other diseases can cause EIS such as dysfunctional breathing disorders, insufficient fitness level, chronic cough, or rare aetiologies **(figure 1)**.(7, 8) Dysfunctional breathing (DB) disorders are abnormal biomechanical patterns of breathing classified as either extrathoracic (e.g. inducible laryngeal obstruction (ILO)) or thoracic (e.g. pattern disordered breathing).(4, 8) Besides functional causes (e.g. ILO, pattern disordered breathing) dysfunctional breathing can result from structural abnormalities such as laryngomalacia.(9, 10) The diagnosis in children with EIS is complicated by possible coexistence of the different causes (11). When investigating children with EIS a thorough history, physical examination and additional diagnostic procedures are essential. Spirometry and measurement of exhaled nitric oxide are helpful to diagnose asthma, particularly combined with a bronchodilator test.(12) The exercise-challenge test is helpful to reproduce exercise-induced bronchoconstriction or other symptoms reported by the patient and to diagnose ILO.(13) Cardiopulmonary exercise testing monitors gas exchange during exercise and is typically used for proving hyperventilation or an insufficient fitness level, and invasive testing such as flexible laryngoscopy allows to directly visualise laryngeal function during exercise.(1)

Prolonged duration of EIS can lead to physical activity avoidance,(14, 15) reduced quality of life,(16) and overtreatment with inhaled corticosteroids if mistakenly diagnosed as asthma.(6, 17) Only few studies have investigated diagnostic practices and diagnoses given to children seen specifically for EIS(7, 17-21), and all have focused on selected groups of

patients excluding children with asthma. No studies have reported the prevalence of different diagnoses and diagnostic practices in representative samples of children with EIS of any cause. We analysed data from Swiss paediatric respiratory outpatient clinics to compare the diagnosis proposed by the referring primary care physician with the diagnosis received at the paediatric respiratory outpatient clinic, and describe diagnostic investigations and treatment prescribed before and at the outpatient clinic.

Methods

Study design

We used data from the Swiss Paediatric Airway Cohort (SPAC), an observational national multi-centre clinical cohort from Switzerland.(22) The study included children aged 0-16 years who were referred to the general paediatric respiratory outpatient clinic of participating hospitals for respiratory problems such as wheeze, cough, dyspnoea, sleep- or exercise-related symptoms and spoke sufficient German to participate. Recruitment for SPAC started in July 1, 2017 and is ongoing. By the time we extracted data for this analysis (October 22, 2019), SPAC recruited patients from five paediatric respiratory outpatient clinics in Switzerland. Among 2436 children invited, 1405 (58%) agreed to participate. The SPAC study was approved by the Bern Cantonal Ethics Committee (Kantonale Ethikkomission Bern 2016-02176). Written informed consent was obtained from parents and directly from patients older than 13 years. This paper is reported following the STROBE statement.(23)

SPAC study procedures and data sources

Eligible patients were recruited at their first clinical visit, where a physician explained the SPAC study. Parents filled in a questionnaire before or shortly after the visit including

information on symptoms, medication, environmental exposures and health behaviours. After the visit, the SPAC study team collected referral letters with information on referral diagnosis, and outpatient clinic letters with information on symptoms history, previous treatments, physical examination, diagnostic tests done, and final diagnosis. Results from diagnostic tests were collected from the clinic records and all information was entered into a Research Electronic Data Capture (REDCap) database.(24)

Inclusion criteria

We included children who were referred for EIS as main referral reason. We considered EIS as main reason for referral if the referral letter or the first outpatient clinic letter described EIS as the only or main reason for referral (**supplementary file 1**). We excluded children with missing information on referral reason or missing final diagnosis.

Referral diagnosis

Referral diagnosis was the diagnosis described as suspected cause of EIS in the referral letter from the referring physician. Suspected referral diagnoses were categorised into three categories: asthma (including asthma, recurrent wheeze, or exercise-induced bronchoconstriction); DB (including extrathoracic or thoracic DB); or unknown aetiology if no suspected diagnosis was described.

Final diagnosis given at outpatient clinic

Final diagnosis was defined as the diagnosis described in the outpatient clinic letter that was sent back to the referring physician after completion of the diagnostic evaluation (which sometimes required more than one visit). Combinations of diagnoses were considered

where coexisting diagnoses were listed. We grouped diagnoses into seven categories suggested in previous publications (4, 8) (**figure 1**). Asthma, extrathoracic DB, thoracic DB, asthma plus any DB, chronic cough, insufficient fitness level, and other diagnoses. We grouped DB into extrathoracic DB (functional: induced laryngeal obstruction, and structural: laryngomalacia, subglottic stenosis) and thoracic DB (functional: pattern disordered breathing, hyperventilation, sighing). For some analyses, we merged rare diagnoses (insufficient fitness level, chronic cough other diagnoses) into one category (**supplementary file 1**). The final diagnosis was categorised as suspected if the diagnosis in the outpatient clinic letter included the word "suspected".

Diagnostic tests performed at outpatient clinic

We extracted information on diagnostic testing from the outpatient clinic letter. Tests included: spirometry, body plethysmography, bronchodilator test, fraction of exhaled nitric oxide (FeNO), allergy tests (skin prick test or specific IgE), chest x-ray, and bronchial challenge tests such as methacholine and exercise-challenge test. Diagnostic tests were performed according to published guidelines (25-27). Challenge tests were often performed at a follow-up visit and we therefore collected challenge tests also from follow-up visits. Children withheld short acting beta2-agonists (SABA) for 8 hours, inhaled corticosteroids (ICS), leukotriene antagonists, and long acting beta2-agonists (LABA) for 24 hours, and antihistamines and sodium cromoglycate for 72 hours before the outpatient clinic visit. All tests were performed by experienced lung function technicians who also assessed quality of the tests.

Prescribed treatments and other variables

We extracted information about treatment taken prior to the first outpatient clinic visit from the referral letter (described by referring physician) and the first outpatient clinic letter (described in clinical history). Treatment prescribed at the outpatient clinic was taken from the outpatient clinic letter with the latest data and summarised as: SABA, ICS, and LABA or combinations. Information on referral to physiotherapy or other specialty and any planned follow-up visits were taken from the outpatient clinic letter. Information about age, sex, height and weight was taken from the outpatient clinic letter. We calculated body mass index (BMI) as weight (kg) / height*height (cm) and calculated age-adjusted BMI z-scores based on reference values from the World Health Organisation (28), defining overweight as BMI z-score > 1 and obesity as BMI z-score > 2. We used information on parental education, environmental factors and physical activity from the standardised parental questionnaire.

Statistical analysis

We compared referral diagnosis with final diagnosis, and described asthma treatment prescribed before and at the outpatient clinic. We compared characteristics of children receiving the different diagnoses using chi-square, fisher's exact and ANOVA tests. Our dataset had few missing values of which the variables parental education (7%) and BMI (2%) had most, and we reported these variables only for children who had valid information. Our main factors of interest (diagnostic evaluations, diagnosis and treatment) had no missing values. We used STATA version 14 for statistical analysis.

Results

Of the 1065 children who had their first outpatient visit after June 1, 2017, 214 (20%) had EIS as main reason for referral (**supplementary file 2**). We included data from five clinics. The

largest clinic contributed 71 patients and the smallest 26 patients (**table 1**). On average, children were 12 years old (SD: 3) and 99 (46%) were female (**table 2**). The commonest referral diagnosis was asthma in 126 (59%); 12 (6%) were suspected to have DB and no diagnosis was proposed in 74 (35%). 89 (43%) had at least one follow-up visit. The average time between baseline and last visit was 3.7 months (range 0.4-16.8).

Final diagnoses from the outpatient clinic letter included asthma (n=115, 54%); extrathoracic DB (n=35, 16%); thoracic DB (n=22, 10%); asthma plus any DB (n=23, 11%), insufficient fitness level (n=10, 5%), chronic cough (n=6, 3%), and other (pleural effusion n=1, unknown aetiology n=2) (**table 3**). Of the 35 children diagnosed with extrathoracic DB, 32 had functional DB (ILO) and 3 had structural DB. Of the 21 with thoracic DB, all had functional DB (pattern disordered breathing n=16, hyperventilation n=2, sighing tics n=4). In the 23 with asthma plus DB, 19 had asthma plus ILO and 4 had asthma plus pattern disordered breathing. The relative frequency of diagnoses differed between clinics (**table 1, supplementary file 3**). Children diagnosed with DB or asthma plus DB were slightly older, more often female, and had a lower BMI z-score than children diagnosed exclusively with asthma or other diagnoses. The referral diagnosis often differed from the final diagnosis. Of the 126 referred for suspected asthma, 37 (29%) got another diagnosis at the outpatient clinic (**table 2, figure 2**). In most (10 of 12) children referred for suspected DB, the diagnosis was confirmed at the outpatient clinic. Of the 76 children with no suspected referral diagnosis, only 24 (32%) were diagnosed with asthma, the majority (n=41) were diagnosed with DB.

The diagnostic tests most often performed at the first outpatient clinic visit were spirometry in 208 (97%), body plethysmography in 171 (80%), and FeNO in 199 (93%) (**table 1, supplementary file 4**). A methacholine challenge test was performed in 50 (23%) and an exercise challenge in 80 (37%). Cardiopulmonary exercise tests or flexible laryngoscopy were not performed. Diagnostic procedures differed by clinic and diagnosis. Children diagnosed with thoracic DB performed exercise-challenge more often (68%) than children diagnosed with EIB (37%) (**table 2**).

Prior to referral, 65% of all children were on inhaled asthma therapy (30% SABA as needed, 2% ICS and 33% on SABA/ICS or LABA/ICS combinations (**table 3**). After evaluation at the outpatient clinic, ICS +/-SABA or ICS+LABA was prescribed almost exclusively to children with asthma or asthma plus any DB. SABA alone was mostly prescribed in children with asthma (30%) or asthma plus any DB (22%), but also in those with extrathoracic DB (17%), thoracic DB (9%), and other diagnoses (26%). 42 children (20%) were referred to physiotherapy for breathing/speech training and all of them were diagnosed with extrathoracic or thoracic DB or asthma plus any DB. Follow-up visits were planned in most children (78%) diagnosed with asthma, but only in 23% children diagnosed with extrathoracic DB and 9% with thoracic DB.

Discussion

This multicentre study of children referred for EIS found that in almost half of the children the diagnosis was revised at the clinic. The commonest final diagnoses apart from asthma were extrathoracic and thoracic DB. Relative frequency of final diagnoses and the set of diagnostic tests performed differed between clinics.

Strengths and limitations

This pragmatic study is the first to report diagnostic evaluation and management in a real-life clinical setting in children referred to respiratory outpatient clinics for any type of EIS. The broad inclusion criteria (children referred for any type of EIS as main reason for referral) ensured a wide clinical spectrum of children with EIS. Recruitment from five different outpatient clinics in Switzerland made it possible to report on clinical practices and to study variations between different tertiary clinics. A resulting weakness is that diagnostic evaluation and description of final diagnosis were not standardised between clinics, which may influence prevalence estimates. The final diagnosis described in the outpatient clinic letter was described as suspected in 97 (45%), indicating uncertainty in the final diagnosis. In these children, the final diagnosis could change after further diagnostic evaluations, which would influence the prevalence of the estimates.

Comparison with other studies and interpretation

We identified six previous studies reporting diagnoses given to children seen for exercise-induced symptoms However all six studies included children with EIS unlikely to be caused by asthma **(supplementary file 5)**.(7, 17-19, 21, 29) In our study we included all children with EIS without excluding those with suspected asthma, and for this reason a larger proportion was diagnosed with asthma (57%) compared with previous studies (8-22% asthma). We found that 33 (15%) were diagnosed with ILO, which in previous studies varied between 3-30%. Thoracic DB (e.g. hyperventilation syndrome, sigh dyspnoea, cough), accounted for 10% in our study. In previous studies it varied both in regard to prevalence (4-34%) and labelling of diagnoses, making comparisons difficult. In two previous studies, many patients (19-67%) were diagnosed as having no disease, because their symptoms represented a

normal physiological response to exercise with a normal fitness level.(7, 19) In our study, none were diagnosed with normal physiological response to exercise, but ten children were diagnosed with insufficient fitness level. The frequency of diagnoses in our study differed from previous studies, but also differed considerably between clinics (e.g. extrathoracic DB varied from 7% in clinic4 to 47% in clinic3). This suggests a lack of agreement on how to diagnose and define different diagnoses between clinics.

In most children referred for EIS, basic investigations for asthma were performed including measurement of FeNO, allergy tests and lung function testing (spirometry and body plethysmography). Further tests that are diagnostic for other diseases than asthma were done in a minority of children. Exercise challenge testing, recommended to reproduce symptoms in patients with EIS,(4, 26, 30) was only done in 37%. By the time of data collection, none of the clinics performed flexible laryngoscopy and cardiopulmonary exercise test, although laryngoscopy is considered the reference standard for diagnosing extrathoracic DB and cardiopulmonary exercise test is used to diagnose hyperventilation syndrome and insufficient fitness level.(12, 31-33) We found that diagnostic investigations differed between clinics, especially methacholine (0-65%) and exercise challenge tests (7-71%). This indicates little agreement on which diagnostic investigations should be done. Further studies should investigate the optimal algorithm for diagnosing children seen for EIS.

Asthma treatment depends on severity (34) and is therefore expected to differ between children. We would have expected that 100% of the children with asthma would have been prescribed some sort of bronchodilator but in our study, it was only in 93%. Apart from children with asthma, 20% of patients diagnosed with extrathoracic DB were prescribed

SABA, which was unexpected but could indicate diagnostic uncertainty. For DB, physiotherapy or speech therapy are recommended treatment.(4, 5) In our study, only half of the children diagnosed with isolated DB (extrathoracic or thoracic) were referred to physiotherapy/speech therapy. The reason for this could be that the pediatric pulmonologist considered the disease as mild and selected a wait-and-see policy after careful instructions about the benign aetiology of the symptoms. Most children diagnosed with asthma (78%) had a planned follow-up visit, but only 23% with extrathoracic DB and 9% with thoracic DB had a planned follow-up visit at the clinic.

In summary, we found that final diagnosis given at the outpatient clinic differed in half of the children from the suspected referral diagnosis. DB was a relatively common diagnosis but rarely suspected by the referring physician. Diagnostic evaluation, management and follow-up were inconsistent between clinics and diagnostic groups. This highlights the need for diagnostic guidelines in children seen for EIS.

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Statement of Ethics

The SPAC study was approved by the Bern Cantonal Ethics Committee (Kantonale Ethikkomission Bern 2016-02176). Written informed consent was obtained from patients' parents or directly from patients at the age of 14 years and older.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author's contributions

EP, CA, CdJ, MG and CK made substantial contributions to the study conception and design. EP drafted the manuscript. EP and CdJ collected and prepared data from the SPAC study. EP, CdJ, CA, AJ, AM, DM, NR, FS, MG, and CK critically revised and approved the manuscript.

Availability of data and material

The SPAC dataset is available on reasonable request by contacting Claudia Kuehni by email: Claudia.kuehni@ispm.unibe.ch .

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Figure 1: Classification of causes of exercise-induced symptoms used in this study

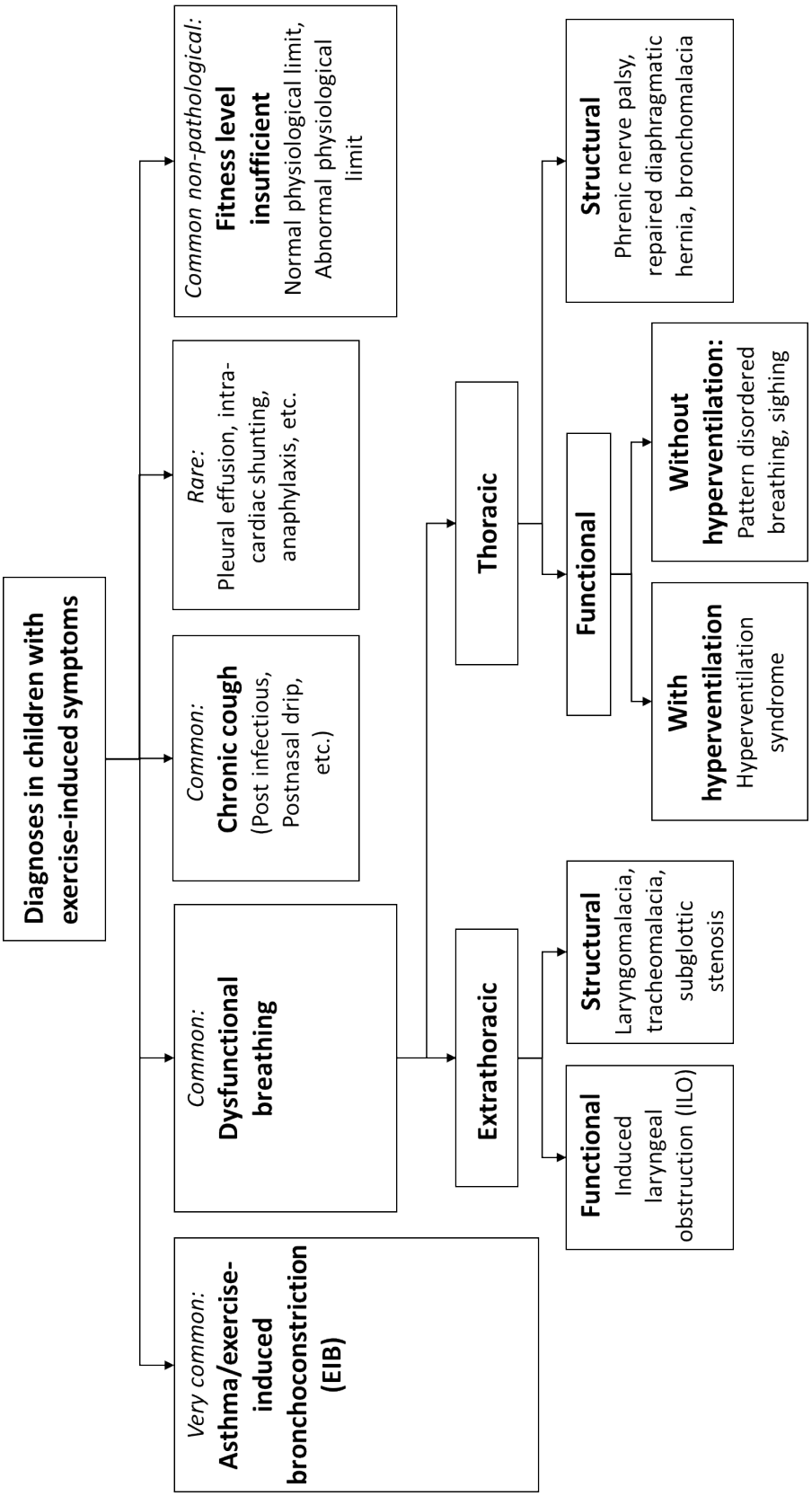


Table 1: Suspected referral diagnosis, final diagnosis and diagnostic tests described in outpatient clinic letter, in total and by centre (N=214)

	Total N=214	Clinic1 N=71	Clinic2 N=56	Clinic3 N=33	Clinic4 N=26	Clinic5 N=28
Referral diagnosis						
Suspected asthma	126 (59)	42 (59)	37 (66)	14 (43)	20 (77)	13 (46)
Suspected DB	12 (6)	3 (4)	5 (9)	4 (12)	0	0
No suspected diagnosis	76 (35)	26 (37)	14 (25)	15 (45)	6 (23)	15 (54)
Final diagnosis from clinic						
Asthma	115 (54)	37 (52)	33 (59)	12 (36)	16 (62)	17 (61)
Extrathoracic DB	35 (16)	13 (18)	10 (18)	6 (18)	1 (4)	5 (18)
Thoracic DB	22 (10)	5 (7)	4 (7)	10 (30)	1 (4)	2 (7)
Asthma + DB	23 (11)	7 (10)	5 (9)	3 (9)	7 (27)	1 (4)
Insufficient fitness level	10 (5)	4 (6)	3 (9)	2 (6)	0	1 (4)
Chronic cough	6 (3)	4 (6)	0	0	1 (4)	1 (4)
Other[a]	3 (1)	1 (1)	1 (2)	0	0	1 (4)
Final diagnosis described as suspected in clinical record	97 (45)	35 (49)	21 (37)	12 (38)	8 (31)	21 (75)
Diagnostic tests done at 1st visit						
Spirometry	208 (97)	67 (94)	56 (100)	33 (100)	25 (96)	27 (96)
Body plethysmography	171 (80)	54 (76)	38 (68)	30 (94)	23 (88)	26 (93)
Bronchodilator test (n=207)	106 (51)	23 (34)	39 (70)	25 (78)	6 (24)	13 (48)
FeNO	199 (93)	61 (86)	53 (95)	33 (100)	25 (96)	27 (96)
Allergy test (skin prick, specific IgE)	124 (58)	51 (72)	32 (57)	4 (13)	20 (77)	17 (61)
Thorax x-ray	17 (8)	5 (7)	8 (14)	0	3 (12)	1 (4)
Diagnostic tests done at 1st or 2nd visit						
Bronchial challenge test (any)	121 (57)	45 (63)	25 (45)	24 (73)	21 (81)	6 (21)
Methacholine challenge	50 (23)	30 (42)	1 (2)	0	15 (58)	4 (14)
Exercise challenge	80 (37)	20 (28)	25 (45)	24 (73)	8 (31)	3 (11)

DB: Dysfunctional breathing, ILO: Inducible laryngeal obstruction, SABA:Short acting beta2 agonist ICS:Inhaled corticosteroids LABA: Long acting beta2; FeNO: Fraction of exhaled nictric oxide [a]EIS of unclear aetiology (n=6), laryngomalacia (n=1), Pleural effusion (n=1) [b]Cardiology, Immunology, Endocrinology, Allergology, Sleep study, other

Table 2: Patient characteristics, referral reason, asthma treatment prior to first visit and diagnostic tests performed at outpatient clinic by final diagnosis

Characteristics	Total	Asthma	Extra-thoracic DB	Thoracic DB	Asthma + DB	Other	P-value[a]
	N=214	N=115	N=35	N=22	N=23	N=19	
Demographics							
Age (years), mean (SD)	12 (3)	11 (3)	12 (3)	13 (2)	13 (2)	10 (4)	<0.004
Sex (female)	99 (46)	44 (38)	23 (66)	12 (55)	16 (70)	4 (21)	0.001
BMI zscore, mean (SD)	0.4 (1.1)	0.6 (1.1)	0.3 (1.0)	0.3 (0.9)	-0.2 (1.0)	0.9 (1.4)	0.030
Sports apart from school (n=203)	172 (85)	95 (86)	29 (91)	18 (86)	18 (82)	12 (71)	0.415
Referral reason							<0.001
Asthma/EIB	126 (59)	89 (77)	12 (34)	3 (14)	14 (61)	8 (42)	
Dysfunctional breathing	12 (6)	2 (2)	7 (20)	3 (14)	0	0	
EIS with unknown aetiology	76 (35)	24 (21)	16 (46)	16 (73)	9 (39)	11 (58)	
Asthma treatment prior to first visit[b]							c
No previous treatment	75 (35)	28 (24)	18 (51)	14 (64)	6 (26)	9 (47)	
SABA only	64 (30)	37 (32)	7 (20)	7 (32)	9 (39)	4 (21)	
ICS only	4 (2)	2 (2)	0	1 (5)	0	1 (5)	
ICS+LABA/SABA	70 (33)	48 (42)	10 (29)	0	8 (35)	4 (21)	
Any inhaler (SABA, ICS or LABA)	138 (65)	87 (76)	17 (49)	8 (38)	17 (74)	9 (47)	
Diagnostic tests done at 1st visit[g]							
Spirometry	208 (98)	113 (99)	35 (100)	22 (100)	23 (100)	15 (79)	<0.001
Body plethysmography	171 (81)	96 (84)	26 (74)	18 (82)	20 (87)	11 (58)	0.095
Bronchodilator test	106 (51)	64 (57)	16 (46)	10 (45)	12 (52)	4 (27)	0.316
FeNO	199 (93)	111 (97)	32 (91)	21 (95)	20 (87)	15 (79)	0.014
Allergy test	124 (58)	72 (63)	18 (51)	8 (36)	15 (65)	11 (58)	0.241
Thorax x-ray	17 (8)	5 (4)	1 (3)	0	3 (13)	8 (42)	<0.001
Diagnostic tests done at 1st or 2nd visit							
Bronchial challenge test (any)	121 (57)	48 (42)	25 (71)	18 (82)	18 (78)	12 (63)	<0.001
Methacholine challenge	50 (23)	25 (22)	8 (23)	6 (29)	7 (30)	4 (21)	0.851
Exercise challenge	80 (37)	25 (22)	18 (51)	15 (68)	13 (57)	9 (47)	<0.001
Treatment prescribed at clinic							
No inhaled treatment prescribed	73 (34)	8 (7)	28 (80)	20 (91)	4 (17)	13 (68)	<0.001
SABA alone as needed/before exercise	52 (24)	34 (30)	6 (17)	2 (9)	5 (22)	5 (26)	0.332
SABA + ICS+/-LABA	54 (25)	47 (41)	0	0	7 (30)	0	<0.001
ICS+/-LABA alone	35 (16)	26 (23)	1 (3)	0	7 (30)	1 (5)	0.001
Referral to:							
Physiotherapy/speech therapy	42 (20)	0	20 (57)	11 (50)	11 (48)	0	<0.001
Other specialty[d]	18 (8)	11 (10)	2 (6)	3 (14)	0	2 (11)	0.437
Follow-up visit planned at clinic	116 (54)	90 (78)	8 (23)	2 (9)	13 (57)	3 (16)	<0.001

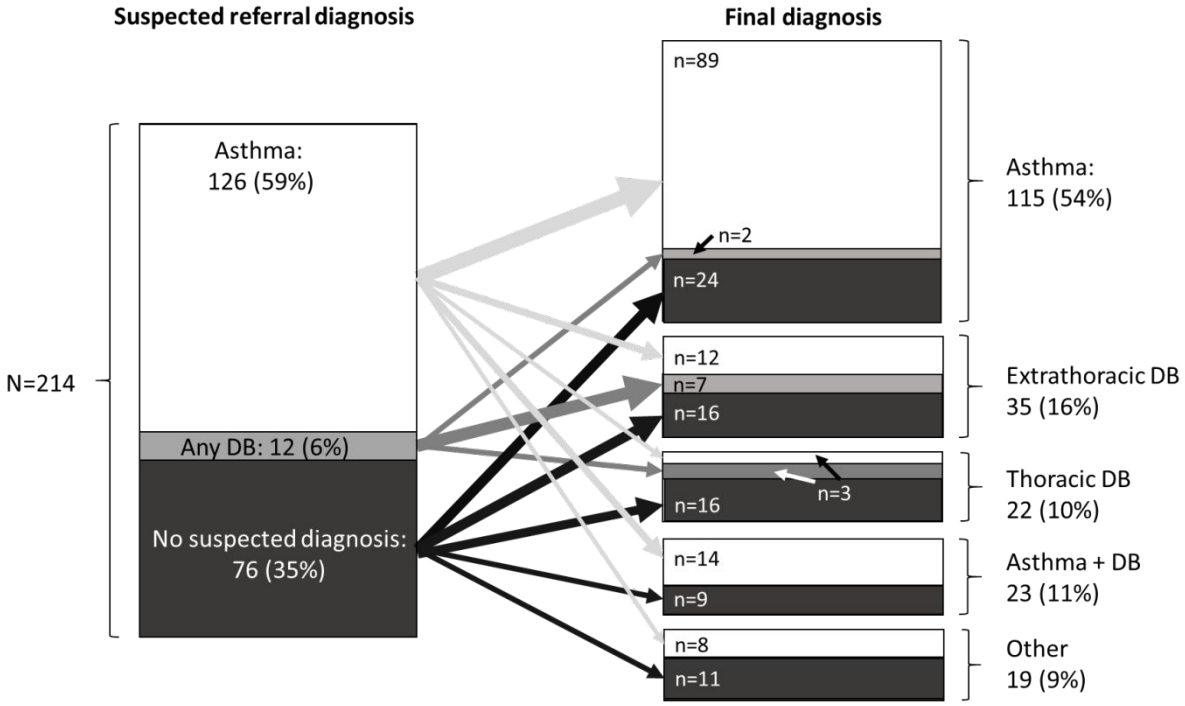
Abbreviations: DB: dysfunctional breathing; EIB: exercise-induced bronchoconstriction; SABA:Short acting beta2 agonist ICS:Inhaled corticosteroids LABA: Long acting beta2; FeNO: Fraction of exhaled nictric oxide; [a]P-value from overall tests performed for difference between diagnosis groups (Fisher's exact for all except age (ANOVA) and sex (Chi-square) [b]Information extracted from referral letters and first outpatient clinic letter [c]too many degrees of freedom and too few observation in single cells [d]Cardiology, endocrinology, allergology, other

Table 3: Diagnosis given at outpatient clinic **(N=214)**

Diagnosis	**n(%)**
Asthma	
Asthma/EIB	115 (54)
Extrathoracic DB	
Functional	
ILO	32 (15)
Structural	
Laryngomalacia	1 (0)
Tracheomalacia	1 (0)
Adenoid hyperplasia	1 (0)
Thoracic DB	
Functional	
PDB (n=16)	16 (7)
Hyperventilation (n=2)	2 (1)
Sighing tics (n=3)	4 (2)
Structural	0
Asthma + DB	
Asthma+extrathoracic functional DB (ILO)	19 (9)
Asthma+thoracic functional DB (PDB)	4 (2)
Insufficient fitness level	
Insufficient fitness level	10 (5)
Chronic cough	
Chronic cough unknown aetiology	4 (2)
Post-infectious chronic cough	2 (1)
Other	
Bilateral pleural effusion	1 (0)
Unknown aetiology	2 (1)

Abbreviations: DB dysfunctional breathing, ILO induced laryngeal obstruction, PDB pattern disordered breathing

Figure 2: Distribution of suspected referral diagnosis (suspected asthma, suspected dysfunctional breathing (DB), no suspected diagnosis) and final diagnosis (asthma, dysfunctional breathing (DB), asthma + DB, other) with proportions (white, grey, black) indicating relationship between suspected referral diagnosis and final diagnosis.

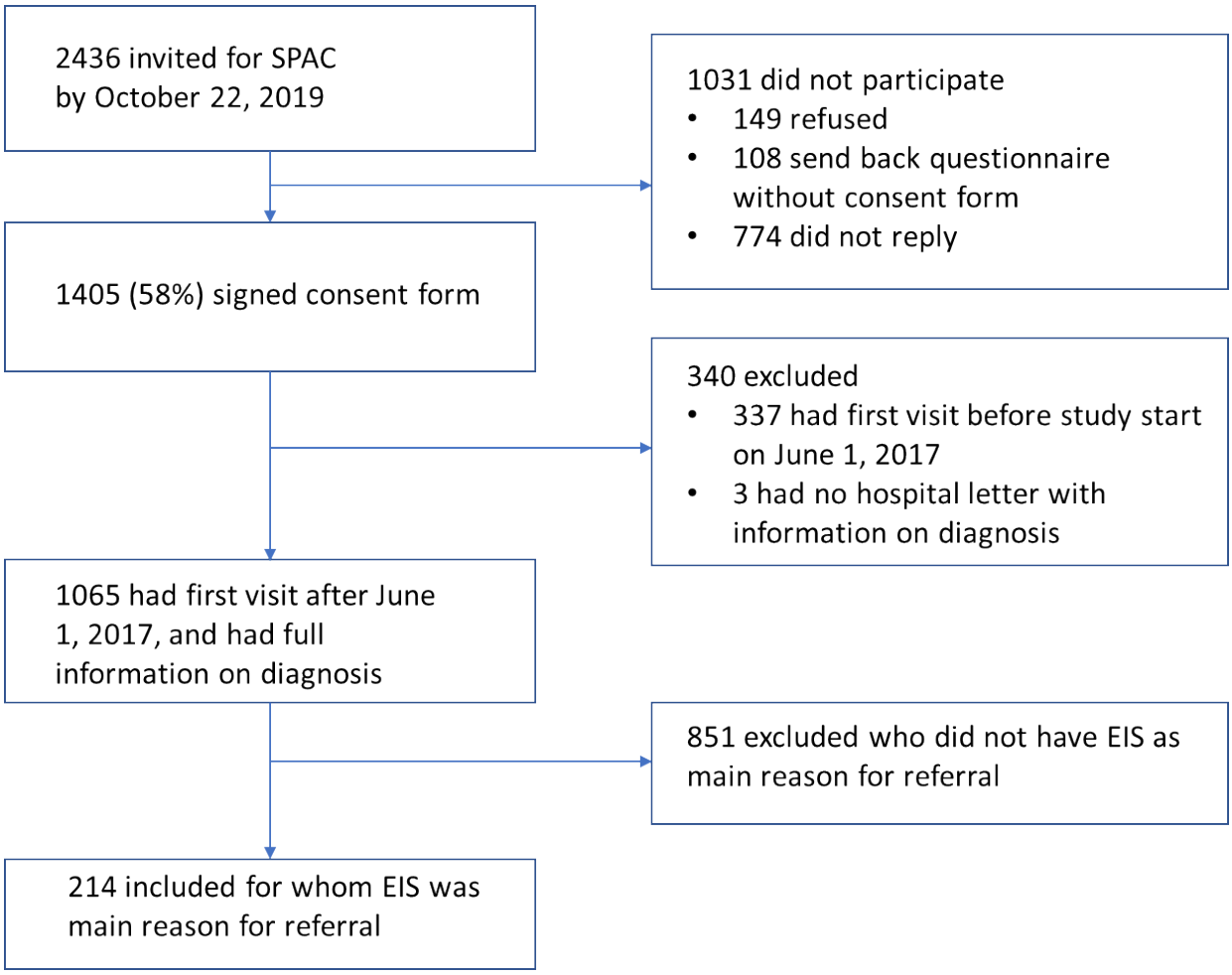


Supplementary file 1: Definitions of variables extracted from referral letters and outpatient clinic letter (terms translated from German)

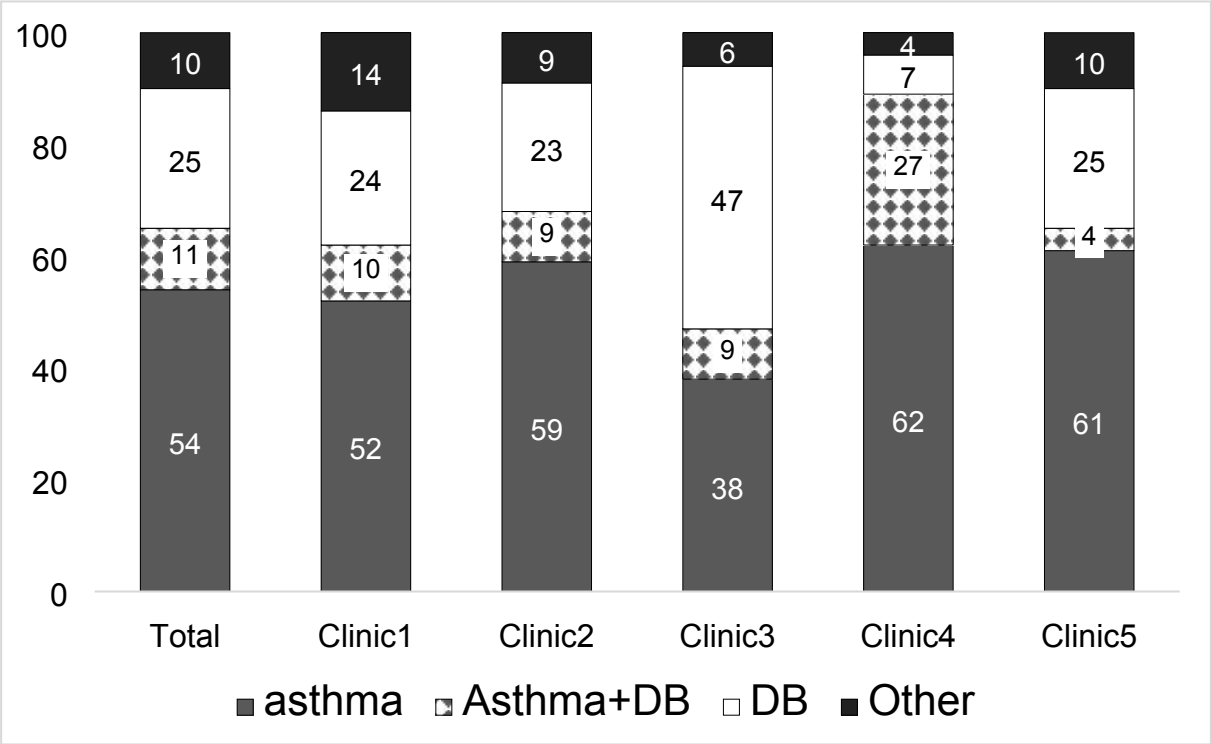
Category	Definition
Referral diagnosis	**If referral letter or first outpatient clinic letter described referral reason as:**
Suspected asthma/EIB	Asthma, exercise-induced asthma, recurrent wheeze, or recurrent obstructive bronchitis
Suspected dysfunctional breathing	Any kind of dysfunctional breathing including terms such as vocal cord dysfunction, inspiratory laryngeal obstruction, hyperventilation syndrome, dysfunctional breathing, etc.
No suspected diagnosis	Exercise-related problems with no suggested aetiology
EIS as main reason for referral	**If referral letter or first outpatient clinic letter described EIS as**
	Single reason for referral
	As first reason for referral with no proceeding descriptions seeming more important than EIS
	Exhaustion-asthma, exercise-induced asthma, exercise-related asthma, exercise-related dyspnoea, exercise-related cough
Final diagnosis[a]	**If outpatient clinic letter described diagnosis as:**
Asthma (obstructive airway disease)	Asthma, preschool-asthma, recurrent wheeze, recurrent obstructive bronchitis, bronchoconstriction
Extrathoracic DB	Vocal cord dysfunction, inspiratory laryngeal obstruction, paradoxical vocal fold motion disorder
Thoracic DB	Dysfunctional breathing with no specification of type of dysfunctional breathing, dysfunctional breathing of thoracic type with insufficient ventilation*. Hyperventilation syndrome, dysfunctional breathing with hyperventilation episodes. Sighing tics
Asthma + DB	Asthma, recurrent wheeze, preschool asthma plus any type of dysfunctional breathing
Insufficient fitness level	Low fitness level as reason for EIS
Chronic cough	Post-infectious chronic cough, chronic cough due to post nasal drip, chronic cough with unknown aetiology
Other	Laryngomalacia, Pleural effusion; unknown aetiology

Abbreviations: EIB: exercise-induced bronchocontristion; EIS; exercise-induced symptoms; DB: dysfunctional breathing; [a]Categories of dysfunctional breathing disorders were defined based on two publications: Depiazzi, Breathe, 2016 and Grüber, Kinder- und Jugendmedizin, 2015 *In German: Insuffiziente Ventilation bei thorakaler Atmung (DATIV)

Supplementary file 2: Flow chart of patients included in analysis

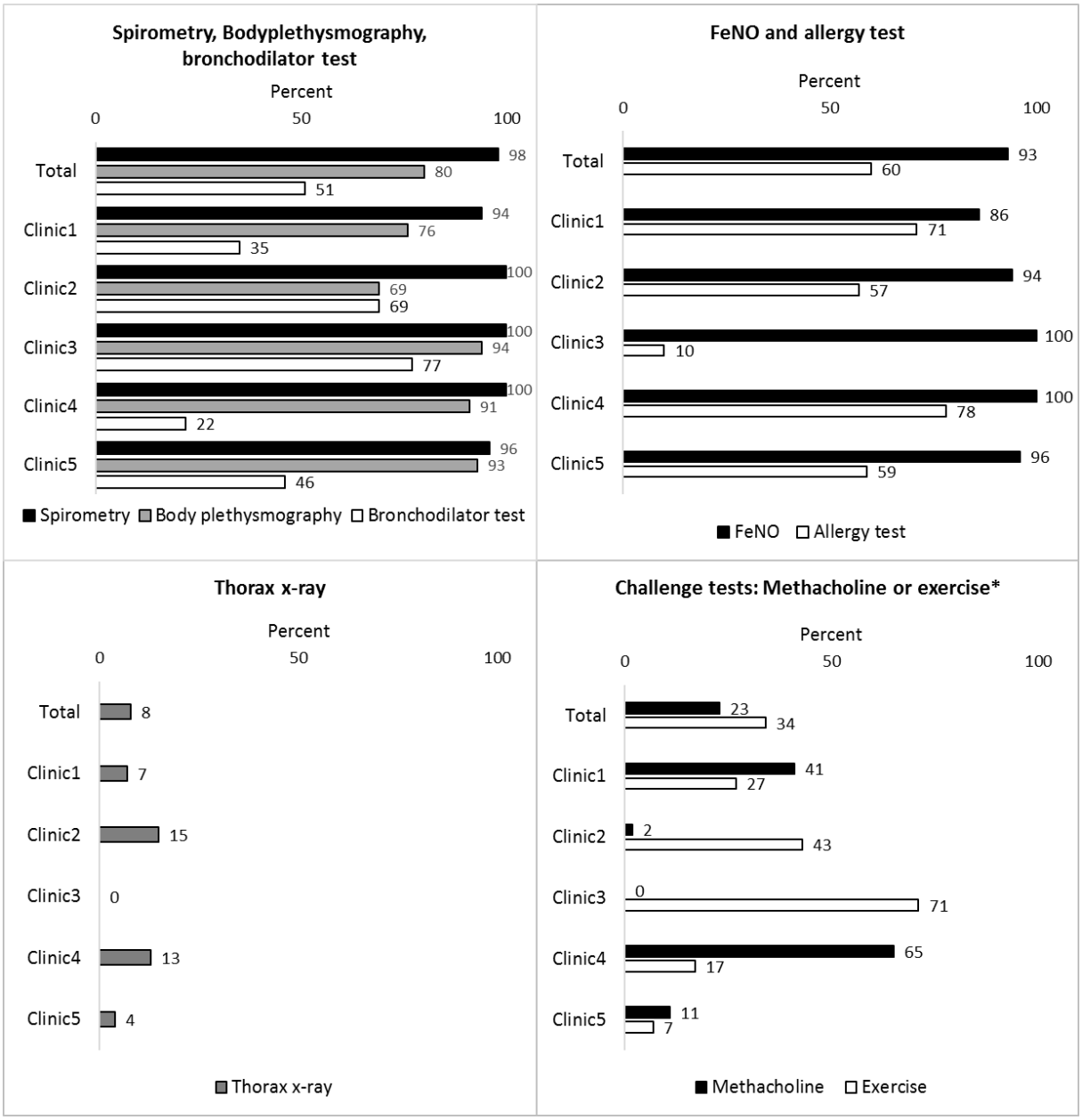


Supplementary figure 3: Final diagnosis given to children referred for exercise-induced respiratory symptoms in total population and by clinic



Abbreviations: DB: Dysfunctional breathing, ILO: Inspiratory laryngeal obstruction.

Supplementary file 4: Diagnostic tests performed at outpatient clinic at first visit after referral (spirometry, bodyplethysmography, bronchodilator test, FeNO, allergy test, thorax x-ray) or first or second visit after referral (methacholine- or exercise-challenge test) in total population and by outpatient clinic.



Abbreviations: FeNO fraction of exhaled nitric oxide *Oxygen uptake and carbon dioxide production was not measured during exercise (no cardiopulmonary exercise test), only spirometry was performed before and after exercise by treadmill or ergonometer.

Supplementary file 5: Studies describing diagnosis given to children referred to outpatient clinics for exercise-induced symptoms

Author, year, journal	Study design, country	Inclusion criteria, N, mean age (range/standard deviation (SD))	Procedure	Final diagnosis as described in paper
Studies including patients referred for EIS unlikely to be caused by asthma				
Abu-Hasan, 2005, Ann Allergy Asthma Immunol (1)	Retrospective chart review of patients referred to pediatric pulmonary and allergy clinic, USA. Month of recruitment = 84	Patients referred for exercise-induced dyspnoea who had no clinically apparent cause or who were treated for exercise-induced asthma without benefit. N=142, mean age (range): 14 (6-21)	Clinical history and physical examination. Pulmonary function, treadmill exercise challenge. Additional electrocardiography, pulse oximetry and breath-by-breath analysis of oxygen utilization and CO2 was measured. Flexible laryngoscopy was performed in patients who showed signs of upper airway obstruction.	11 (8%): asthma 13 (9%): vocal cord dysfunction 2 (1%): exercise-induced laryngomalacia 15 (11%): thoracic cage abnormalities (scoliosis and pecturs deformities) 74 (52%): normal physiologic response to exercise 25 (18%): no symptoms reproduced, no diagnosis
Mahut, 2014, Pediatric Pulmo-nology (2)	Prospective cross-sectional study of consecutively referred patients, France. Month of recruitment = 18.	Children and adolescents (no athletes) with exertional dyspnea that lasted 4 weeks, normal baseline spirometry and chest radiography and no response to rapid beta-agonist preventive therapy. N=79, mean age (SD): 12 (2)	Clinical history. Cardiopulmonary exercise test with salbutamol administered 15 min before testing. Among others minute ventilation, oxygen uptake and CO2 was measured.	17 (22%): asthma 2 (3%): Vocal cord dysfunction 3 (4%): Alveolar hyperventilation syndrome 7 (9%): Poor conditioning 53 (67%): Normal physiological response to exercise
Seear, 2005, Arch Dis Child (3)	Prospective review of consecutively referred patients, Canada. Month of recruitment = 18	Patients referred to pediatric pulmonology clinic with a complaint of poorly controlled asthma. N=52, mean age (SD): 12 (3)	Clinical history and spirometry before and after exercise-challenge testing (at 5 and 15 minutes).	8 (15%): asthma 14 (27%): Vocal cord dysfunction /sigh dyspnoea 7 (14%): Habit cough 12 (23%): poor physical fitness 11 (21%) no diagnosis
Hammo, 1999, Ann Allergy Asthma Immunol (4)	Retrospective chart review, USA. Month of recruitment = 12	Patients referred to pediatric pulmonary division for exertional dyspnoea or chest tightness without a clear history of asthma and/or where the history suggested that symptoms were not controlled with an inhaled beta-2 agonist. N=32, mean age (age range): 13 (8-18)	Clinical history and treadmill exercise-challenge test and pulse oximeter to measure end-tidal O2 and CO2. Running at 85% of aerobic capacity for 6 minutes. Spirometry performed before and after (at 2, 5, 10 and 15 minutes) Pulse oximetry and end-tidal CO2 were monitored after exercise until stable.	4 (13%): Asthma 11 (34%): hyperventilation 17 (53%): no reproducible symptoms; no diagnosis. .
Studies including patients referred for EIS suspected of having ILO				
Hseu, 2016, Int J Pediatr Otorhi-nolryngol (5)	Retrospective chart review of patients evaluated at pediatric hospital exercise clinic, USA. Month of recruit-ment = 96	Patients complaining of shortness of breath with exercise, suspected of having vocal cord dysfunction or paradoxical vocal cord dysfunction. N=294, mean age: 15	Pre and post- treadmill exercise pulmonary function tests (2-4 minutes heart rate at 85% of max, 4-6 minutes heart rate above 85% of max) and laryngoscopic examinations were performed during the visit.	30 (10%): asthma 86 (30%): vocal fold dysfunction 29 (10%): deconditioning. 54 (19%) (normal) physiologic dyspnoea 24 (8%): no clear diagnosis
Buchwald, 2016, Pediat Pulmonol ((6)	Prospective review of consecutively referred patients, Denmark. Month of recruitment = 54	Patients with exercise-induced inspiratory symptoms referred from asthma centres. N=54, mean age 14 (9-18)	Continuous lyrangoscopy exercise (CLE) during maximum exercise on treadmill.	18 (33%) positive CLE test (diagnosi: ILO) 28 (52%) negative CLE (diagnosis: not described) 5 (9%) inconclusive CLE test (diagnosis: 2 unknown, 1laryngeal nerve paralysis, 1 laryngomalacia, 1 subglottic stenosis)

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7.3 Publication 3: Symptoms differentiate diagnoses in children with exercise-induced respiratory symptoms – findings from the Swiss Paediatric Airway Cohort (SPAC)

Pedersen ESL, de Jong CCM, Ardura-Garcia C, Mallet MC, Jochmann A, Moeller A, Mueller-Suter D, Regamey N, Singer F, Goutaki M, Kuehni CE.

Original article

Own contribution: Conceptualise and design study, prepare and analyse data, interpret results, draft manuscript and display items.

Reported symptoms differentiate diagnoses in children with exercise-induced respiratory problems: findings from the Swiss Paediatric Airway Cohort (SPAC)

Authors

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Disclosure statement

The authors declare that they have no competing interests.

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Statements for JACI in practice

1. What is already known about this topic?

Exercise-induced breathing problems of variable aetiology can have similar clinical presentations complicating diagnosis although experts have suggested symptoms that are helpful to distinguish differential diagnoses, however their usefulness has not been formally evaluated. (33/35 words)

2. What does this article add to our knowledge?

Parent reports descriptions of exercise-induced symptoms (type of symptoms, onset of symptoms, triggers, and effect of treatment) help to differentiate diagnoses in children with exercise-induced respiratory problems. (28/35 words)

3. How does this study impact current management guidelines?

Our results emphasize the importance of taking a detailed symptoms history in children with exercise-induced problems and suggest which questions are most helpful. (16/35 words)

Key words

Exercise-induced, ILO, asthma, EIB, asthma, childhood

List of abbreviations

BMI	Body mass index
DB	Dysfunctional breathing

EIS	Exercise-induced symptoms
ILO	Inducible laryngeal obstruction
RRR	Relative risk ratio
SPAC	Swiss Paediatric Airway Cohort

Abstract (255 words)

Background: Exercise-induced breathing problems of different origin can have similar clinical presentations which can make it difficult to distinguish common diagnoses such as asthma, extrathoracic and thoracic dysfunctional breathing.

Aims: We studied which parent-reported exercise-induced symptoms (EIS) are useful to distinguish different diagnoses of EIS in children seen in respiratory outpatient clinics.

Methods: This study was nested in the Swiss Paediatric Airway Cohort (SPAC), an observational study of children aged 0-17 years referred to paediatric respiratory outpatient clinics in Switzerland. In this analysis, we included children aged 6-17 years with available information on symptoms and diagnosis. We used multinomial regression to study how parent-reported symptoms from a questionnaire differed between diagnoses.

Results: 702 (66%) of 1071 children reported EIS in the questionnaire (mean age 11 years, 305 (43%) female). Dyspnoea was the type of EIS that best distinguished diagnoses. Dyspnoea was reported most often for thoracic DB (RRR 5.3, 95%CI 1.2-22) compared with asthma. Of exercise triggers, swimming best distinguished: thoracic DB (RRR 2.8, 95%CI 1.3-6.1) and asthma plus DB (RRR 2.1, 95%CI 1.1-4.1) from isolated asthma. Late onset of EIS (after exercise compared to during exercise) was less common for extrathoracic DB (RRR 0.1, 95%CI 0.02-0.5) and thoracic DB (RRR 0.4, 95%CI 0.1-1.2) compared with asthma. Localisation of dyspnoea (throat vs. chest) differed between extrathoracic DB (RRR 2.4, 95%CI 1.0-6.0) and asthma. Reported respiration phase (in- or expiration) did not distinguish diagnoses.

Conclusion: This study showed that parent-reported symptoms help to distinguish different diagnoses in children with EIS highlighting the importance for physicians to take a detailed history.

Manuscript: 2492 words

Introduction

Exercise-induced symptoms (EIS) are common in childhood but the underlying cause can be difficult to identify because EIS of different origin can have an overlapping clinical presentation (1-3). EIS are most often caused by exercise-induced bronchoconstriction and extrathoracic or thoracic dysfunctional breathing (DB) but there is a range of other causes, including insufficient fitness level and unspecific chronic cough (4, 5). Despite similar clinical presentations, certain symptoms are typically associated with specific diagnoses (6-8). Knowing which of the symptoms are particularly helpful to distinguish different underlying causes of EIS may lead to faster diagnosis. For instance, expiratory wheeze, cough, and shortness of breath are typical for exercise-induced bronchoconstriction, with symptoms lasting from minutes to hours and usually peaking after exercise (9, 10). Inspiratory problems with stridor, throat tightness, and shortness of breath are more typical for extrathoracic DB with symptoms lasting only minutes and peaking during exercise (9, 11). Typical symptoms for thoracic DB are shortness of breath, sighing, dizziness and symptoms can last from minutes to hours and peak during exercise (12). Tingling in fingers or lips is typical for thoracic with hyperventilation. For unspecific chronic cough, symptoms depend on the underlying cause of the cough (13).

Misdiagnosis in children with EIS occurs, especially in children with extrathoracic DB, which might be reduced if we know better which symptoms are particularly helpful to distinguish diagnoses (14-16). Few original studies examined the association of diagnoses with typical symptoms. They reported EIS only for specific diagnostic groups (e.g. asthma) (17), or compared two diagnosis groups only (e.g. asthma compared with ILO) (18-20). We studied

children visiting paediatric outpatient clinics in Switzerland to investigate which symptoms reported by parents in a questionnaire are most useful to distinguish different diagnoses of EIS.

Method

Study design

We used data from the Swiss Paediatric Airway Cohort (SPAC), a multi-centre study of children referred to paediatric respiratory outpatient clinics in Switzerland (21). The SPAC study included children aged 0-17 years who were referred for respiratory problems such as wheeze, cough, dyspnoea, sleep- or exercise-related symptoms and spoke sufficient German to participate. At the time of the visit, the physicians explained the SPAC study to the families. Parents filled in a questionnaire before or shortly after the visit including information on symptoms, medication, environment and health behaviours. After the visit, the SPAC study team collected the outpatient clinic letters that had been sent back to the referring paediatrician with information on diagnosis, diagnostic investigations and treatment. Questionnaires and information from outpatient clinic letters were entered into a Research Electronic Data Capture (REDCap) database (22). Recruitment for SPAC started in July 2017 and is ongoing. By the time we extracted data for this analysis, eight paediatric respiratory outpatient clinics in Switzerland were participating. Among 2504 children invited, 1414 (59%) agreed to participate (November 15, 2019). The SPAC study was approved by the Bern Cantonal Ethics Committee (Kantonale Ethikkomission Bern 2016-02176). Written informed consent was obtained from parents and patients older than 13 years. This paper is reported following the STROBE statement (23).

Inclusion criteria

We included children aged 6-17 years with a completed baseline questionnaire and an available outpatient clinic letter with information on diagnosis. We restricted the population to schoolchildren because nearly all children referred for EIS to respiratory outpatient clinics are older than 5 years. The question used to identify children with EIS was “Does your child sometimes experience breathing problems during exercise?”.

Parent reported exercise-induced symptoms (EIS)

The questionnaire asked about type of symptoms and characteristics of symptoms. Type of symptoms included exercise-induced wheeze, cough, dyspnoea, tingling sensation in fingertips/lips, and other symptoms (with a free text field to specify). Characteristics of symptoms included trigger factors (running, bicycle riding, intensive sport games, and swimming), localisation of dyspnoea (chest, throat, or both), respiration phase (inspiration, expiration), onset of EIS (during or after exercise), duration of symptoms, and whether a short-acting bronchodilator helped to relieve symptoms. Exact wording of questions from the questionnaire is in **supplementary table 1**.

Diagnosis

Diagnosis was taken from the outpatient clinic letter that the hospital pulmonologists sent back to the referring physician. Some children were seen more than once in the outpatient clinic, and we took the diagnosis from the outpatient clinic with the latest date. We distinguished six diagnoses of EIS: asthma, extrathoracic DB, thoracic DB, asthma plus DB, chronic cough, and other (including insufficient fitness level, EIS of unknown aetiology, allergic rhinoconjunctitivitis, recurrent respiratory infections, rare pulmonary diseases).

Exact definitions of diagnoses are in **Supplementary table 2**. If children had more than one diagnosis listed in the letter, we used the first listed, except in children who had asthma and any type of DB. In these children we created a separate category (asthma plus DB) as we believed that symptoms might differ between children with isolated asthma, isolated DB, and the combination of both.

Other variables

Information about age, sex, height and weight was taken from the outpatient clinic letter. We calculated body mass index (BMI) as weight / height^2 (kg/m^2) and calculated age-adjusted BMI z-scores based on Swiss reference values (24), defining overweight as BMI z-score > 1. We took information on symptoms (other than those induced by exercise), parental education, environmental factors, and physical activity from the parental questionnaire.

Statistical methods

We compared proportions of EIS by diagnosis categories: asthma, extrathoracic DB, thoracic DB, asthma plus DB, chronic cough, and other using chi-square and Fisher's exact tests. We studied which symptoms were most useful to distinguish diagnoses using multinomial logistic regression. We defined diagnosis as outcome and asthma as the reference category and added one explanatory EIS variable at a time. We adjusted each model for age and sex. For the multinomial regression, we grouped chronic cough with other diagnosis because of the sample size. Overall, we had little missing information in the questionnaire replies (<7%) apart from the question about the respiration phase when EIS are worst (inspiration or expiration) where 14% were missing. We used STATA version 14 for statistical analysis.

Results

Of the 1071 children aged 6-17 whose parents completed the baseline questionnaire and for whom we had information about diagnosis, 705 (66%) answered yes to EIS in the questionnaire (**supplementary figure 1).** On average, children with EIS were 11 years old (SD 3.2), 306 (43%) were female (**table 1**). Compared with children without EIS, those with EIS were older and more often female. The diagnosis given to children with EIS was asthma in 534 (76%), extrathoracic DB in 36 (5%), thoracic DB in 29 (4%), asthma plus DB in 39 (6%), chronic cough in 19 (3%), and other diagnosis in 48 (7%).

Type of EIS differed between diagnosis groups (**figure 1, table 2, figure 2**). Results from our multinomial regression analysis (adjusted for age and sex) showed that wheeze was reported less often for children with other diagnoses (Relative risk ratio (RRR) 0.2, 95% CI 0.1-0.3) than for children with isolated asthma. Cough was less common in children with thoracic DB (RRR 0.3, 95% CI 0.1-0.7) and asthma plus DB (RRR 0.3, 95% CI 0.2-0.6) than children with isolated asthma. Dyspnoea was reported more in children with thoracic DB (RRR 5.3, 95% CI 1.2-22.8) and asthma plus DB (RRR 4.4, 95% CI 1.4-14.7) than in children with isolated asthma. A tingling feeling in fingertips or lips was more common in children with thoracic DB (RRR 3.2, 95% CI 1.3-7.8) and other symptoms (RRR 2.7, 95%CI 1.1-6.7) than in children with isolated asthma.

The type of physical activity reported to trigger EIS differed between diagnosis groups (**table 2**, **figure 3**). Compared with children with asthma, swimming was more commonly reported as trigger in children with thoracic DB (RRR 2.8, 95%CI 1.3-6.1), asthma plus DB (RRR 2.1,

95%CI 1.1-4.1), and other diagnosis (RRR 2.0, 95%CI 1.2-3.4). Bicycle riding was reported more often in children with extrathoracic DB (RRR 2.5, 95%CI 1.2-5.6), and intensive sports games were more often reported in children with asthma plus DB (RRR 3.3, 95%CI 1.1-9.5).

Also characteristics of EIS differed between diagnosis categories (**table 2, figure 4**). Late onset of EIS (after exercise) was rarely reported for extrathoracic DB (RRR 0.1, 95% CI 0.02-0.5) compared with isolated asthma. A long duration of EIS (more than 10 minutes) was reported mostly for children with thoracic DB (RRR 4.7, 95% CI 1.3-16.2) compared with isolated asthma. For localisation of dyspnoea, throat was reported more often than chest for children with extrathoracic DB (RRR 2.4, 95% CI 1.0-6.0) compared with asthma. Respiration phase (inspiration or expiration) did not differ between diagnosis groups. Use of a bronchodilator made symptoms disappear in close to half of the children with asthma (43%) and much less in children with extrathoracic DB (15%), thoracic DB (15%), asthma plus DB (22%), and chronic cough (17%) (**table 2**).

Discussion

This is the first study that investigated which parent-reported symptoms were useful to distinguish different diagnoses in a representative sample of children with EIS referred to respiratory outpatient clinics. We found that reported type of EIS differed between diagnosis groups, especially cough, dyspnoea, and tingling sensation in fingers or lips. Of the physical activities triggering EIS, intensive sport games and swimming best distinguished diagnosis groups. Additionally, onset of symptoms, duration of symptoms, and effect of a short acting bronchodilator differed between the diagnoses categories. Respiration phase (inspiration or expiration) was less helpful.

Strengths and limitations

Our study included detailed information about type of EIS, activities that triggered EIS, and characterisation of symptoms, information that to our knowledge has not been reported in such detail before. Our study is the first to compare detailed questionnaire reported symptoms between several diagnosis groups including asthma, extrathoracic DB, thoracic DB, and the combination of asthma and DB in children with EIS. No studies have yet examined how exercise activities differ trigger different types of exercise-induced problems. In addition, our study was nested in SPAC, a real-life observational clinical cohort study, including a representative sample of children referred to paediatric respiratory outpatient clinics for any type of respiratory problem. Therefore, we think that our findings can be broadly generalised to children seen by respiratory physicians for EIS.

A limitation of the study was that the questionnaire was addressed to the parents rather than the children themselves. However, we encouraged parents to fill in the questionnaire together with their child, which has been shown to increase validity of reported symptoms (25). Our questionnaire did not include separate questions on expiratory wheeze and inspiratory stridor. It has been described that most children with EIS have the sensation that symptoms occur during inspiration rather than expiration, also in children with asthma (5). This might explain why we found no difference in whether symptoms were worst during inspiration or expiration between diagnosis groups. This question has also relatively many missing answers, which indicates that parents were unable to answer. Our limited sample size for some diagnostic categories (thoracic DB, n=27) reflected relatively wide confidence intervals, and we could not investigate how combinations of reported symptoms distinguish

diagnoses in children with EIS. Our study is, however, the largest of its kind to study how symptoms differ between children with variable underlying causes of EIS. A further limitation is that the final diagnosis was made by different pulmonologist and not based on a standardised predefined diagnostic algorithm. However, all pulmonologist were board-qualified and diagnoses were based on clinical history and standardized diagnostic tests results.

Comparison with other studies

Only few studies described questionnaire reported symptoms for children or adolescents with EIS. A Swedish population based study in children aged 12-13 years reported exercise-induced symptoms for 128 children with an asthma diagnosis (17). Exercise-induced wheeze was reported for 76 (59%), cough for 81 (63%), and chest tightness for 56 (44%), however also throat tightness was reported for 63 (49%) and inspiratory stridor for 47 (37%). Similar to our results, they found that adolescents with asthma additionally reported throat tightness and inspiratory problems. We overall saw a higher prevalence of all symptoms because we included respiratory outpatients rather than children from the general population. A case series described symptoms in 12 adolescent athletes seen for suspected exercise-induced laryngeal obstruction (EILO) (19). Dyspnoea during inspiration was reported by all (100%) and dyspnoea during expiration by 8 (67%). Throat tightness was reported more frequently (50%) than chest tightness (25%). The same was seen in a Danish study that compared 42 adolescents with EILO (diagnosed using laryngoscopy) with 16 adolescents diagnosed with airway hyperresponsiveness (AHR) (by a methacholine challenge test) (18). They found that both those with EILO and AHR reported wheeze and stridor but adolescents with EILO more often reported cough, chest and throat tightness and adolescents with AHR

more often reported dyspnoea. Our results and those from previous studies emphasize that no symptom is uniquely reported for single diagnoses among children with EIS, but some symptoms are more often reported for some diagnoses compared to others. The same tendency has been shown in studies reporting on exercise-induced symptoms recorded in hospital records (26-29).

Interpretation

We found that type of reported symptoms (cough, dyspnoea, tingling sensation, and other symptoms) were better in distinguishing thoracic DB from asthma than extrathoracic DB from asthma. This highlights why especially extrathoracic DB is sometimes misdiagnosed as asthma (14, 16). Onset of EIS during exercise was strongly associated with extrathoracic DB, while onset after exercise was associated with asthma. This finding is in line with the literature and could help physicians distinguish extrathoracic DB from asthma (7, 30, 31). We did not see any difference in the duration of symptoms between diagnoses groups. So this question might be less useful. However, the limited usefulness of duration of symptoms may also be because parents have difficulties answering this question. For children with co-existence of asthma and DB, symptoms did not differ strongly from children with isolated asthma, however they less often reported cough and more often reported dyspnoea. In children with asthma who do not cough, but report dyspnoea, physicians should check if the child has DB in addition to asthma.

Conclusion

Diagnosing children with EIS is not easy and requires a thorough diagnostic work up. Parent-reported symptoms (including information on type of symptoms, activities triggering EIS,

and characteristics of symptoms) can help to distinguish different diagnoses in children seen with EIS. This highlights the importance for physicians to take a detailed symptom history.

Ethics approval and consent to participate

The SPAC study was approved by the Bern Cantonal Ethics Committee (Kantonale Ethikkomission Bern 2016-02176). Written informed consent was obtained from parents and directly from patients older than 13 years.

Author's contributions

EP, CA, CdJ, CM, MG and CK made substantial contributions to the study conception and design. EP and CdJ collected and prepared data from the SPAC study. EP drafted the manuscript. EP, CdJ, CA, AJ, AM, DM, NR, FS, MG, and CK critically revised and approved the manuscript.

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Availability of data and material

The SPAC dataset is available on reasonable request by contacting Claudia Kuehni by email: Claudia.kuehni@ispm.unibe.ch .

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Table 1: Comparison of characteristics, respiratory symptoms and diagnoses between patients with and without exercise induced symptoms (EIS) (N=1071)

	Yes to EIS in questionnaire	No to EIS in questionnaire
	N=705	N=366
Characteristics	n(%)	n(%)
Demographic and socioeconomic characteristics		
Age (years), mean (SD)	11.0 (3.2)	9.5 (3.1)
Sex (female)	306 (43)	121 (36)
BMI z-score, mean (SD) (n=1048)	0.3 (1.2)	0.2 (1.2)
Overweight (BMI z-score >1) (n=1048)	177 (26)	76 (23)
Sports apart from at school (n=1056)	541 (77)	246 (69)
Swiss nationality	587 (83)	299 (82)
Parental education		
Mother, tertiary[a] (n=1019)	251 (37)	110 (30)
Father, tertiary[a] (n=1015)	305 (45)	135 (39)
Parental smoking		
Mother, current smoking (n=1053)	112 (16)	49 (14)
Father, current smoking (n=1012)	167 (25)	79 (23)
Respiratory symptoms in the past 12 months		
Cough apart from colds, yes often (n=1060)	87 (12)	53 (15)
Cough at night apart from colds (n=1043)	319 (47)	144 (40)
Wheeze (n=1048)	432 (62)	159 (45)
>3 attacks of wheeze (n=1055)	207 (30)	47 (13)
Rhinitis apart from colds (n=1062)	462 (63)	206 (57)
Eczema ever (n=931)	211 (35)	98 (30)
Diagnosis given at outpatient clinic		
Asthma	534 (76)	268 (73)
Extrathoracic dysfunctional breathing	36 (5)	0
Thoracic dysfunctional breathing	29 (4)	7 (2)
Asthma + any DB	39 (6)	1 (0)
Chronic cough	19 (3)	34 (9)
Other	48 (7)	56 (15)

[a] Degree from university of applied sciences or university. Abbreviations: EIS: exercise induced symptoms

Table 2: Reported exercise-induced symptoms by diagnosis group in children who reported exercise-induced respiratory symptoms in the questionnaire (n=702)

Baseline questionnaire	Asthma N=532 N (%)	DB extra-thoracic N=35 N (%)	DB thoracic N=27 N (%)	Asthma + any DB N=39 N (%)	Cough N=19 N (%)	Other N=50 N (%)	P-value
Type of symptoms[a]							
Wheeze (n=696)	317 (60)	19 (54)	14 (52)	25 (64)	10 (29)	5 (16)	<0.001
Cough (n=696)	380 (72)	18 (51)	12 (44)	16 (41)	28 (82)	18 (58)	<0.001
Dyspnoea (n=696)	364 (69)	30 (86)	26 (96)	36 (92)	16 (47)	20 (65)	<0.001
Tingling feelings in finger or lips (n=638)	51 (11)	6 (17)	8 (32)	7 (19)	3 (10)	7 (23)	0.005
Other symptoms (n=696)	57 (11)	5 (14)	8 (30)	8 (21)	4 (12)	8 (26)	0.016
Trigger activities (n=672)							
Run short (50-100 m)	318 (66)	26 (72)	19 (69)	26 (67)	12 (67)	34 (76)	0.522
Run far (>1 km)	390 (77)	32 (89)	21 (75)	32 (82)	12 (67)	32 (71)	0.360
Cycle	254 (50)	27 (75)	19 (68)	23 (59)	9 (50)	24 (53)	0.034
Intensive sport games[#]	385 (75)	27 (75)	22 (76)	35 (90)	12 (67)	32 (71)	0.353
Swim	155 (31)	13 (36)	16 (57)	20 (51)	6 (33)	23 (51)	0.001
Localisation of dyspnoea (n=473 of 492 with dyspnoea)[b]							
Chest	182 (52)	14 (47)	11 (44)	19 (56)	3 (33)	19 (73)	0.183
Throat	47 (13)	9 (30)	6 (24)	4 (12)	3 (33)	3 (12)	
Chest and Throat	120 (34)	7 (23)	8 (32)	11 (32)	3 (33)	4 (15)	
Respiration phase[c] (n=600)							
Inspiration	209 (46)	17 (50)	11 (44)	24 (63)	10 (43)	12 (46)	*
Expiration	45 (10)	0	2 (8)	2 (5)	2 (9)	2 (8)	
Inspiration and Expiration	200 (44)	17 (50)	12 (48)	12 (32)	11 (48)	12 (46)	
EIS start[d] (n=648)							<0.001
During exercise	332 (68)	34 (97)	22 (85)	31 (82)	15 (44)	21 (70)	
After ending exercise	153 (32)	1 (3)	4 (15)	7 (18)	19 (56)	9 (30)	
Duration of EIS[e] (n=648)							0.391
1-2 minutes	181 (37)	13 (37)	4 (17)	13 (35)	12 (38)	15 (48)	
5-10 minutes	262 (53)	19 (54)	13 (57)	22 (59)	15 (47)	14 (45)	
Longer than 10 min	47 (10)	3 (9)	6 (26)	2 (5)	5 (16)	2 (6)	
Used asthma-spray before or during exercise?[g] (n=683)	400 (77)	14 (40)	13 (46)	33 (87)	19 (56)	14 (45)	<0.001
Effect of asthma-spray[h] (n=453)							
EIS disappear	165 (43)	2 (15)	2 (15)	7 (22)	3 (17)	1 (8)	*
EIS are reduced	201 (52)	8 (62)	9 (69)	17 (53)	10 (56)	8 (67)	
No effect	22 (6)	3 (23)	2 (15)	8 (25)	5 (28)	3 (25)	

. This table is displaying n(%) with column percentages [a]Which symptoms does your child have during exercise? [b]If reported dyspnoea: Where is the sensation of symptoms felt the strongest? [c]When are the symptoms worst? [d]When do the symptoms begin? [e]After ending the exercise, how long do the symptoms usually stay? [f]Does your child sometimes get a tingling sensation in fingertips or around the mouth during the EIS? [g]Has your child ever used an asthma-inhaler during EIS? [h]How well does this asthma-inhaler help? *To few observations in single cells to calculate Fisher's exact

Figure 1: Types of EIS displayed by diagnosis group (asthma, extrathoracic DB, thoracic DB, asthma + any DB, chronic cough, other diagnosis) among children who reported EIS in the questionnaire (n=702)

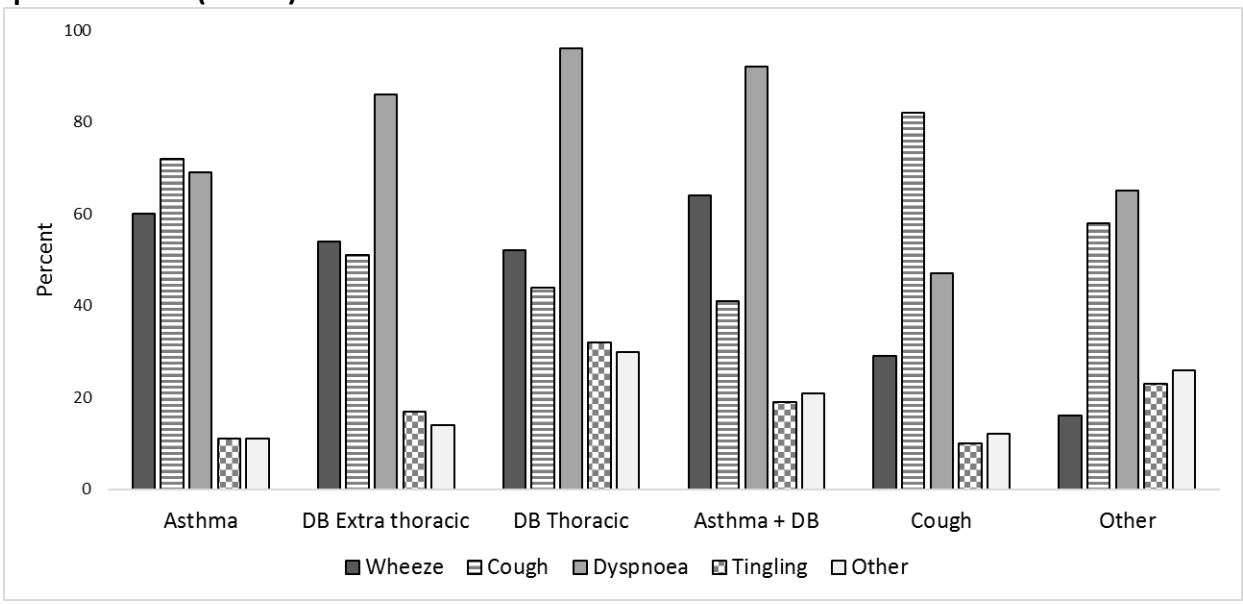
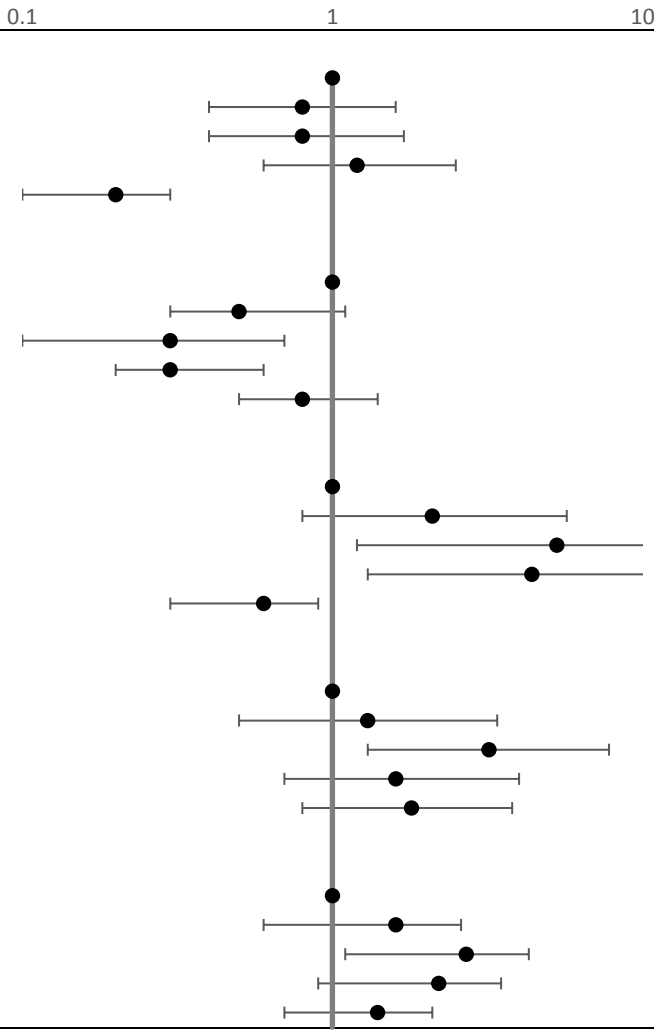


Figure 2: Differences in type of reported symptoms between different diagnosis categories for children with EIS

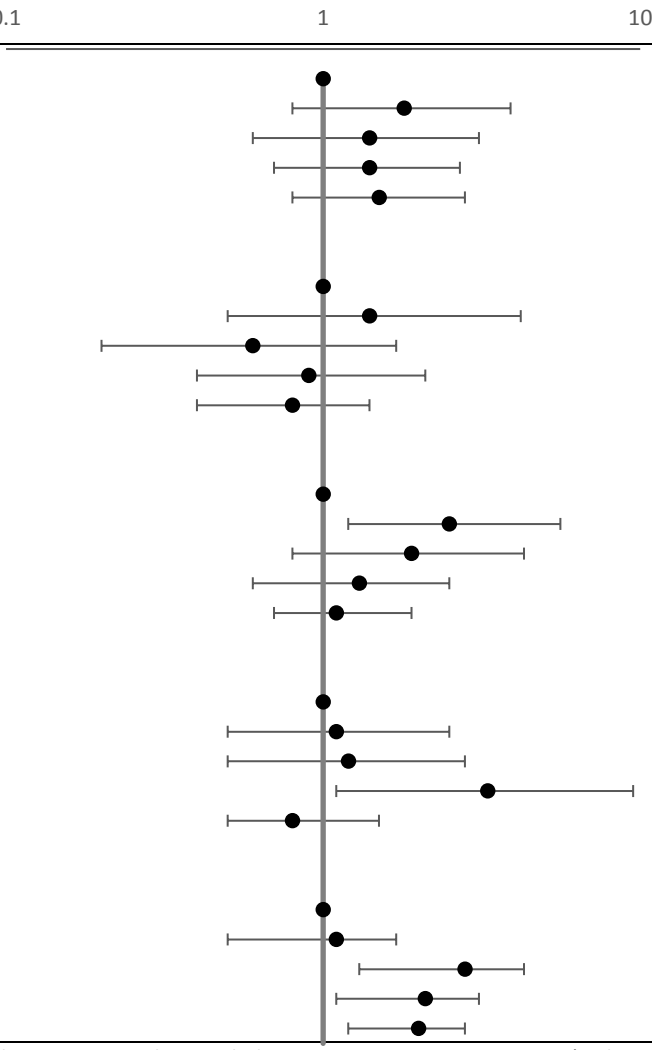
	RRR	95%CI
Wheeze		
Asthma (base)	1	
Extrathoracic DB	0.8	0.4 - 1.6
Thoracic DB	0.8	0.4 - 1.7
Asthma + DB	1.2	0.6 - 2.5
Cough + other	0.2	0.1 - 0.3
Cough		
Asthma (base)	1	
Extrathoracic DB	0.5	0.3 - 1.1
Thoracic DB	0.3	0.1 - 0.7
Asthma + DB	0.3	0.2 - 0.6
Cough + other	0.8	0.5 - 1.4
Dyspnoea		
Asthma (base)	1	
Extrathoracic DB	2.1	0.8 - 5.7
Thoracic DB	5.3	1.2 - 22.8
Asthma + DB	4.4	1.3 - 14.7
Cough + other	0.6	0.3 - 0.9
Tingling feeling		
Asthma (base)	1	
Extrathoracic DB	1.3	0.5 - 3.4
Thoracic DB	3.2	1.3 - 7.8
Asthma + DB	1.6	0.7 - 4.0
Cough + other	1.8	0.8 - 3.8
Other		
Asthma (base)	1	
Extrathoracic DB	1.6	0.6 - 4.3
Thoracic DB	2.7	1.1 - 6.7
Asthma + DB	2.2	0.9 - 5.4
Cough + other	1.4	0.7 - 2.7



The graphs represent relative risk ratios from multinomial regression analysis with diagnosis categories as outcome (asthma as base variable) and type of symptoms (wheeze, cough, dyspnea, tingling sensation in fingertips/lips, other symptoms) adjusted for age and sex. RRR: Relative risk ratio, 95%CI: 95% confidence interval, DB dysfunctional breathing

Figure 3: Differences in reported activities triggering EIS between different diagnosis categories for children with EIS

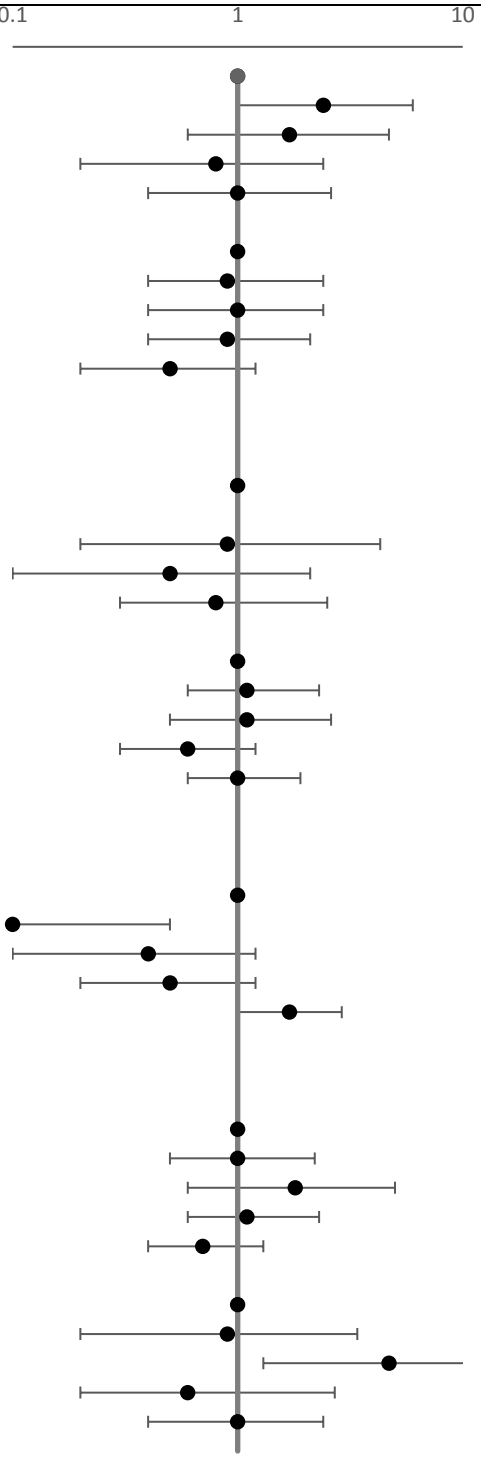
	RRR	95%CI
Run short distance (50-100 m)		
Asthma (base)	1	
Extrathoracic DB	1.8	0.8 - 3.9
Thoracic DB	1.4	0.6 - 3.1
Asthma + DB	1.4	0.7 - 2.7
Cough + other	1.5	0.8 - 2.8
Run long distance (>1 km)		
Asthma (base)	1	
Extrathoracic DB	1.4	0.5 - 4.2
Thoracic DB	0.6	0.2 - 1.7
Asthma + DB	0.9	0.4 - 2.1
Cough + other	0.8	0.4 - 1.4
Bicycle riding		
Asthma (base)	1	
Extrathoracic DB	2.5	1.2 - 5.6
Thoracic DB	1.9	0.8 - 4.3
Asthma + DB	1.3	0.6 - 2.5
Cough + other	1.1	0.7 - 1.9
Intensive sport games		
Asthma (base)	1	
Extrathoracic DB	1.1	0.5 - 2.5
Thoracic DB	1.2	0.5 - 2.8
Asthma + DB	3.3	1.1 - 9.5
Cough + other	0.8	0.5 - 1.5
Swimming		
Asthma (base)	1	
Extrathoracic DB	1.1	0.5 - 2.3
Thoracic DB	2.8	1.3 - 6.1
Asthma + DB	2.1	1.1 - 4.1
Cough + other	2.0	1.2 - 3.4



The graphs represent relative risk ratios from multinomial regression analysis with diagnosis categories as outcome (asthma as base variable) and trigger activities (run, cycle, intensive sport games, swim) adjusted for age and sex. RRR: Relative risk ratio, 95%CI: 95% confidence interval, m: meter, km: kilometre, DB dysfunctional breathing

Figure 4: Differences in reported characteristics of EIS between different diagnosis categories for children with EIS

	RRR	95% CI
Localisation		
Throat vs. Chest		
Asthma (base)	1	
Extrathoracic DB	2.4	1.0 - 6.0
Thoracic DB	1.7	0.6 - 4.7
Asthma + DB	0.8	0.2 - 2.4
Cough + other	1.0	0.4 - 2.6
Throat and chest vs. chest		
Asthma (base)	1	
Extrathoracic DB	0.9	0.4 - 2.4
Thoracic DB	1.0	0.4 - 2.4
Asthma + DB	0.9	0.4 - 2.1
Cough + other	0.5	0.2 - 1.2
Respiration phase (reference category: inspiration)		
Expiration		
Asthma (base)	1	
Extrathoracic DB	-	
Thoracic DB	0.9	0.2 - 4.3
Asthma + DB	0.5	0.1 - 2.1
Cough + other	0.8	0.3 - 2.5
Expiration and inspiration		
Asthma (base)	1	
Extrathoracic DB	1.1	0.6 - 2.3
Thoracic DB	1.1	0.5 - 2.6
Asthma + DB	0.6	0.3 - 1.2
Cough + other	1.0	0.6 - 1.9
Onset of EIS		
After exercise vs. during exercise		
Asthma (base)	1	
Extrathoracic DB	0.1	0.02 - 0.5
Thoracic DB	0.4	0.1 - 1.2
Asthma + DB	0.5	0.2 - 1.2
Cough + other	1.7	1.0 - 2.9
EIS duration		
5-10 min vs 1-2 min		
Asthma (base)	1	
Extrathoracic DB	1.0	0.5 - 2.2
Thoracic DB	1.8	0.6 - 5.0
Asthma + DB	1.1	0.6 - 2.3
Cough + other	0.7	0.4 - 1.3
>10 min vs 1-2 min		
Asthma (base)	1	
Extrathoracic DB	0.9	0.2 - 3.4
Thoracic DB	4.7	1.3 - 16.2
Asthma + DB	0.6	0.2 - 2.7
Cough + other	1.0	0.4 - 2.4
Effect of asthma medication	*	



The graphs represent relative risk ratios from multinomial regression analysis with diagnosis categories as outcome (asthma as base variable) and characterisations of symptoms (Localisation of dyspnea, respiration phase, duration of EIS) as explanatory variables. RRR: Relative risk ratio, 95%CI: 95% confidence interval, DB dysfunctional breathing *Too few observations to perform multinomial regression analysis

Supplementary table 1: Questions from the questionnaire asking about exercise-induced symptoms

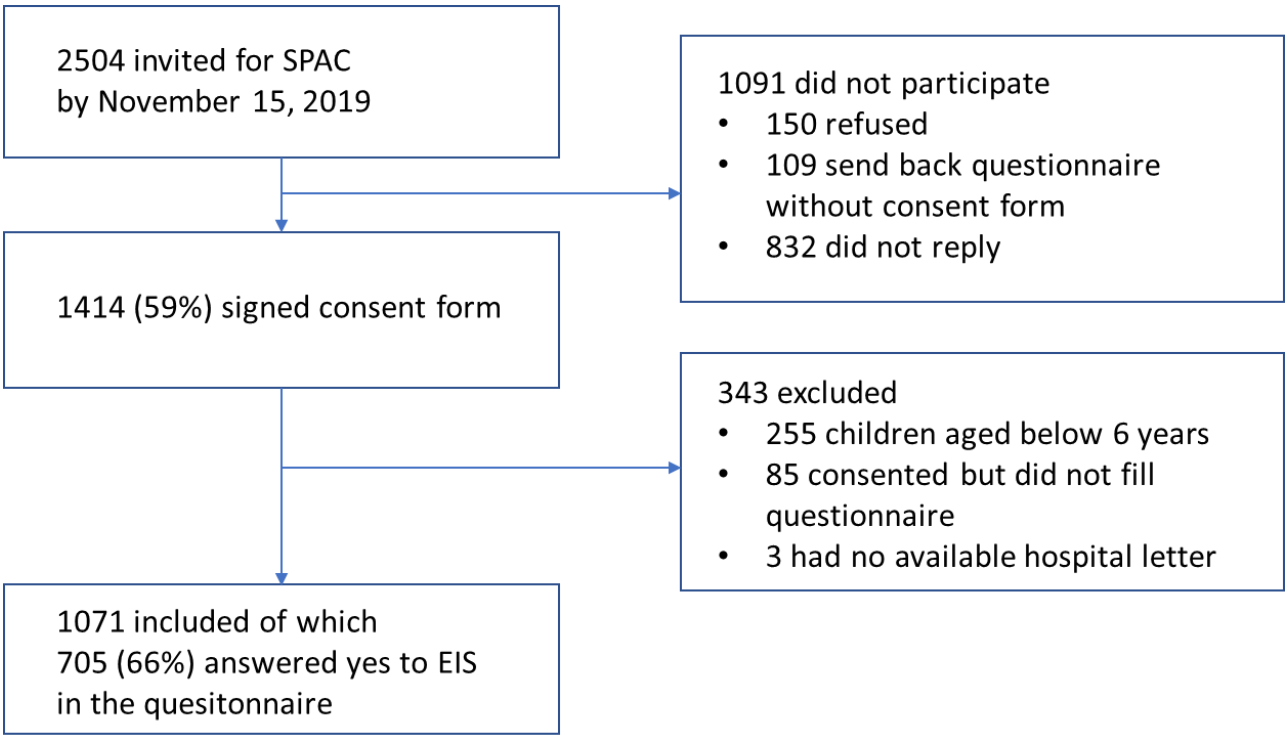
Variable	Question in questionnaire
Any EIS	Does your child sometimes experience breathing problems when exercising? (yes/no)
Wheeze	Which breathing problems does your child experience when exercising? Wheezing or whistling breathing sounds (yes/no)
Cough	Which breathing problems does your child experience when exercising? Cough (yes/no)
Dyspnoea	Which breathing problems does your child experience when exercising? Dyspnoea or tightness (yes/no)
Tingling feeling in fingertips or lips	Does your child sometimes experience a sensation as if ants were creeping around the fingertips or lips while exercising? (yes/no)
Other	Which breathing problems does your child experience when exercising? Other problems (yes/no)
Other, which	If other problems, which? (free text field)
Types of EIS triggers	In which of the following situation, does the breathing problems occur? Running short, middle, longer distances, biking, sport games, swimming
Localisation of dyspnoea	If dyspnoea or tightness, where is the sensation felt the strongest? - Chest - Throat - Everywhere (Chest and throat)
When are EIS worst	When are the breathing problems worst? - During inspiration - During expiration - Equally during inspiration and expiration
EIS start	When do the breathing problems begin? – When you child for example runs a longer distance, then the breathing problems normally begin: - Straight away after the first steps - A few minutes after beginning the exercise - After ending the exercise
Duration	After ending the exercise, how long do the breathing problems normally last (when your child takes no medication)? - Only short, maximum 1-2 minutes - Longer, 5-10 minutes or more - Other, how long? (free text field)
Inhalation for EIS	Has your child inhaled an asthma-spray or asthma-powder for breathing problems occuring when exercising? (yes/no)
Effect of inhalation	If yes: How well does the medication help? - The breathing problems disappear - The breathing problems are reduced - You almost feel no difference

Supplementary table 2: Definitions of diagnosis from outpatient clinic letter

Category	Definition
Final diagnosis[a]	**If outpatient clinic letter described diagnosis as:**
Asthma, EIB	Asthma, preschool-asthma, recurrent wheeze, recurrent obstructive bronchitis, exercise-induced bronchoconstriction
Extrathoracic DB	Vocal cord dysfunction, inspiratory laryngeal obstruction, paradoxical vocal fold motion disorder, laryngomalacia, tracheomalacia
Thoracic DB	Dysfunctional breathing with no specification of type of dysfunctional breathing, dysfunctional breathing of thoracic type with insufficient ventilation*. Hyperventilation syndrome, dysfunctional breathing with hyperventilation episodes, sighing tics, sighing dyspnoea
Asthma + DB	Asthma or EIB (see first category) plus any type of dysfunctional breathing
Chronic cough	Post-infectious chronic cough, chronic cough due to post nasal drip, chronic cough with unknown aetiology
Other	Insufficient fitness level, EIS due to obesity, laryngomalacia, Pleural effusion, unknown aetiology

Abbreviations: EIB: exercise-induced bronchocontristion; EIS; exercise-induced symptoms; DB: dysfunctional breathing; [a]Categories of dysfunctional breathing disorders were defined based on two publications: Depiazzi, Breathe, 2016 and Grüber, Kinder- und Jugendmedizin, 2015 *In German: Insuffiziente Ventilation bei thorakaler Atmung (DATIV)

Supplementary figure 1: Flow chart of study population



Supplementary table 3: Other exercise-induced symptoms (free text responses) reported in baseline questionnaire by diagnosis group (n=93)

Baseline questionnaire	Asthma N=532 N (%)	DB extra-thoracic N=35 N (%)	DB thoracic N=27 N (%)	Asthma + any DB N=39 N (%)	Cough N=19 N (%)	Other N=50 N (%)	P-value
Other symptoms							
Dizziness	9 (15)	2 (40)	2 (25)	5 (56)	0	2 (25)	*
Fast tired	11 (19)	0	1 (13)	0	0	3 (38)	
Chest pain	9 (15)	0	1 (13)	0	1 (25)	0	
Headache	5 (8)	0	1 (13)	1 (11)	0	1 (13)	
Other	25 (42)	3 (60)	3 (37)	3 (33)	3 (75)	2 (25)	

This table is displaying n(%) with column percentages [a]Which symptoms does your child have during exercise? [b]If reported dyspnoea: Where is the sensation of symptoms felt the strongest? [c]When are the symptoms worst? [d]When do the symptoms begin? [e]After ending the exercise, how long do the symptoms usually stay? [f]Does your child sometimes get a tingling sensation in fingertips or around the mouth during the EIS? [g]Has your child ever used an asthma-inhaler during EIS? [h]How well does this asthma-inhaler help?

7.4 Publication 4: Reporting of exercise-induced symptoms by physicians

Pedersen ESL, de Jong CCM, Barben J, Casaulta C, Jochmann A, Marangu DM, Moeller A, Mueller-Suter D, Regamey N, Singer F, Ardura-Garcia C, Kuehni CE.

Original article

Own contribution: Conceptualise and design study, prepare and analyse data, interpret results, draft manuscript and display items.

Reporting of exercise-induced symptoms by physicians Title (max 7 words)

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Disclosure statement

The authors declare that they have no competing interests.

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Abstract (unstructured, max 50 words)

It has been suggested that a detailed history is essential for the differential diagnosis of exercise-induced symptoms (EIS) in children. We studied EIS described in physicians' reports and studied agreement with parental reported EIS from questionnaires. Our results suggest that the contribution of a detailed anamnesis could be better exploited for the differential diagnosis of EIS.

Manuscript 1347 words (max length of manuscript: 9 pages with in-publication display items)

Exercise-induced symptoms are common in childhood and differential diagnosis is not easy. It has been suggested that a detailed history allows to make the diagnosis in a large proportion of cases, because certain symptoms are typically associated with specific diagnoses (1-3). EIS are most often caused by asthma, extrathoracic dysfunctional breathing (e.g. inducible laryngeal obstruction), thoracic dysfunctional breathing (e.g. breathing pattern disorders), or insufficient fitness (4-6). Expiratory wheeze, cough, and chest tightness are common for asthma (7), while inspiratory stridor and dyspnoea are more common for extrathoracic dysfunctional breathing (8). Thoracic dysfunctional breathing is associated with dyspnoea, sighing, and dizziness and may be accompanied by hyperventilation (9). Onset and duration of symptoms and effect of inhaled medication on symptoms are also important information for differentiating diagnoses in children with EIS (2, 8).

To our knowledge no studies have investigated how often and in which detail EIS are asked and reported in medical reports for arguing the likelihood of different differential diagnoses in children presenting with exercise-induced respiratory problems. We therefore studied clinical presentations of EIS reported by physicians in the medical records using data from a multicentre study in children referred to paediatric respiratory outpatient clinics in Switzerland and compared clinical presentation of EIS to parental answers in a standardized questionnaire.

Methods

Study design

We used data from the Swiss Paediatric Airway Cohort (SPAC), an observational multi-centre study of children seen in respiratory outpatient clinics in Switzerland (10). All clinics are led by board-certified paedaitric pulmonologists, and teaching clinics for specialised paediatric pulmonology. The SPAC study includes children aged 0-17 years referred to general paediatric respiratory outpatient clinics for respiratory problems such as wheeze, cough, dyspnoea, sleep- or exercise-related symptoms. Parents filled in a questionnaire before or shortly after the visit including information on symptoms, medication, environmental exposures and health behaviours. Data are also collected from hospital records including referral diagnosis, final diagnosis, diagnostic investigations, and prescribed medication. All data were entered into a Research Electronic Data Capture (REDCap) database (11). Recruitment started in July 2017 and is ongoing. The SPAC study was approved by the Bern Cantonal Ethics Committee (Kantonale Ethikkomission Bern 2016-02176). Written informed consent was obtained from parents and directly from patients older than 13 years.

Inclusion criteria

We included children aged 6-17 years who were referred for EIS as main referral reason. EIS were considered the main reason for referral if the referral letter or the first outpatient clinic letter described EIS as the only or main reason for referral.

EIS reported by physician and parents

EIS reported by the physician were taken from the outpatient clinic letter that was sent back to the referring physician. The outpatient clinic letter typically includes a section describing diagnosis, a section describing previous and current symptoms, and a section where the differential diagnosis is discussed and the most likely diagnosis justified. We extracted whether any symptoms triggered by exercise were described in the clinical history, the type of EIS (e.g. wheeze, cough, dyspnoea, tingling feeling in fingertips or lips, and other symptoms), the localisation (chest, throat), the respiration phase EIS in which symptoms are worst (inspiration, expiration), the onset of EIS (during or after exercise), whether any bronchodilators had been tried and their effect (**supplementary table 1**). EIS reported by the parents were taken from the questionnaire (**supplementary table 1)**.

Final diagnosis

The final diagnosis was taken from the outpatient clinic letter. We grouped diagnoses related to asthma, extrathoracic dysfunctional breathing (e.g. inducible laryngeal obstruction, laryngomalacia), thoracic dysfunctional breathing (e.g. breathing pattern disorders), exercise-induced bronchoconstriction plus dysfunctional breathing (for patients with coexisting diagnoses), and other diagnoses (e.g. insufficient fitness level, chronic cough, or rare pulmonary causes).

Statistical analysis

We compared proportions of physicians reported and parent reported EIS if physicians had reported any information (item not missing in clinical letter), and calculated agreement using Cohen's kappa for dichotomous outcomes and Fleiss' kappa for categorical variables with more than two categories. The kappa was interpreted using Landis and Koch's criteria (12). We also assessed if agreement of EIS depended on who filled in the questionnaire (mother, father, child helped). We used STATA version 14 for statistical analyses.

Results

Of the 1669 children who participated in the SPAC study by October 15, 2019, 196 (12%) were aged 6-17 years and referred primarily for EIS (**supplementary table 2**). The mean age was 12 years and 92 (48%) were girls. The final diagnosis from the outpatient clinic was asthma in 106 (55%), extrathoracic dysfunctional breathing in 33 (17%), thoracic dysfunctional breathing in 21 (11%), asthma plus dysfunctional breathing in 21 (11%), and other diagnosis in 12 (6%).

Physicians reported information on any EIS in 186 (96%) of the children (**table 1**). The type of physical activity that triggered EIS was reported in 69%, localisation of EIS in 48%, respiration phase in 45%, EIS start in 37%, used of bronchodilators in 94%, and their effect in 88%. Overall, any EIS and characteristics of EIS were reported more often by physicians for children finally diagnosed with dysfunctional breathing than for children diagnosed with asthma or other diagnoses (**table 1**).

Overall, parents reported symptoms more often than physicians (**table 2**). For example, exercise-induced cough was reported by physicians in the clinical history for 35% of children, but by parents for 57%. The agreement between physician-reported and parental reported EIS was moderate for use of bronchodilators (k=0.53) and poor to fair for all other symptoms. For type of symptoms, the agreement was best for wheeze (k=0.24) and cough (k=0.39). For type of exercise triggers, agreement was best for swimming (k=0.22) and worst for intensive sport games (k=0.01). Localisation had better agreement (k=0.36) than respiration phase (k=0.13).

Agreement between physician- and parent-reported EIS differed depending on who filled in the questionnaire for single items but agreement was not systematically better for either of the categories (questionnaire filled in by mother, father or other, or child helped).

Discussion

This study is the first to examine details of EIS reported by physicians in specialist letters to referring physicians, and to assess agreement with parent reported symptoms. Due to the observational design of SPAC, this pragmatic study reflects real life in specialist pulmonology consultations in Switzerland. A limitation of our study was that our agreement analyses were based on symptoms reported by the physician as free text while parents were prompted for each question in a questionnaire. This may explain why parents overall report more symptoms than physicians. Another limitation was that the parental questionnaire did not ask about stridor as there is no common word in German. We therefore could not assess agreement between physician-reported and parent-reported wheeze and stridor separately.

To our knowledge, no other studies investigated the reporting of EIS by physicians in the clinical history. Several studies investigated the agreement between patient and physician reported respiratory symptoms and found overall fair to moderate agreement. A study in 1119 adults assessed agreement between symptoms (chest pain, dyspnoea, or cough) reported by physicians in an electronic medical record with symptoms reported by patients in a patient information form (13). They found kappa statistics between k=0.38 and k=0.50. The better agreement compared to our results may be because patients directly reported symptoms, whereas in our study, symptoms were reported by parents. A study using population-based data from the Dutch Generation R study examined the agreement between physician reported prevalence of wheeze (measured by interview using a short, standardized questionnaire) with parent questionnaire-reported wheeze (14). They found that parents more often reported wheeze (36%) than physicians (20%), which is in line with our results.

Conclusion

Detailed symptom descriptions are essential for the differential diagnosis in children with EIS. This has been emphasized in several publications (5, 15, 16). In this study, we found that any EIS were

reported in almost all children referred for EIS, but triggers and detailed descriptions of EIS were reported in around half. Our results indicate that the symptom history reported by physicians might not be exploited fully for diagnosing children with EIS. A semi-structured interview guide for reporting EIS in the clinical history may help improve reporting of EIS in the medical records.

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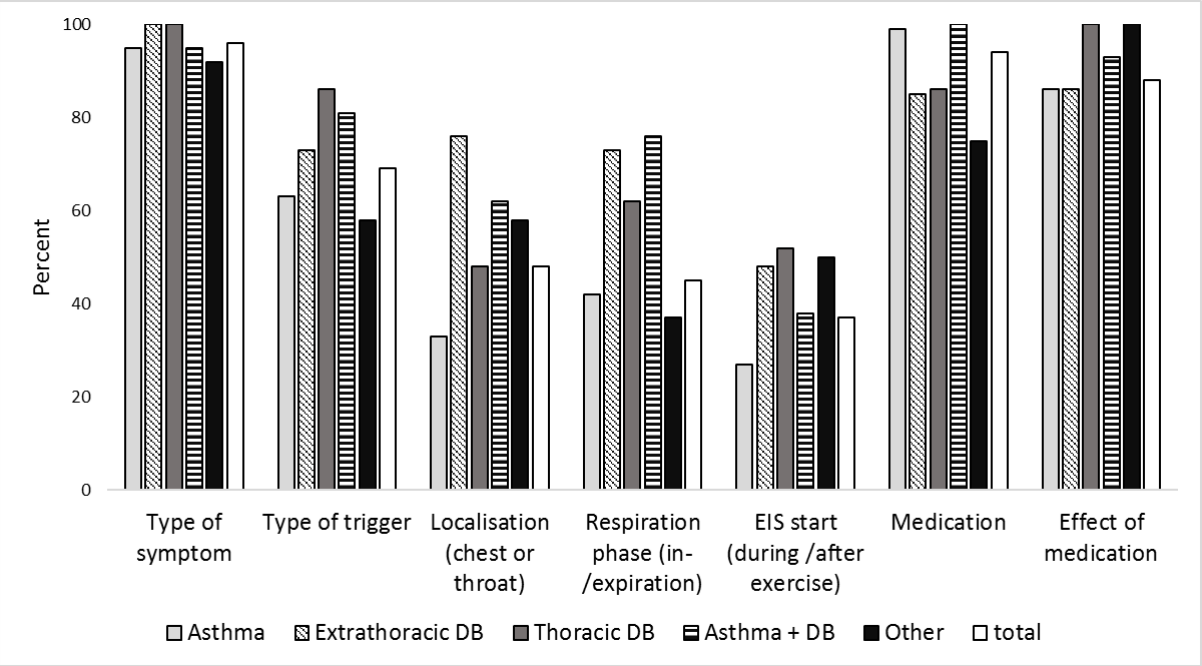
Table 1: Exercise-induced symptoms reported by the physician in the clinical history, in all children and by diagnosis category (n=193)



Any information in outpatient clinic letter on:	Total (n=193)	EIB (n=106)	Extra-thoracic DB (N=33)	Thoracic DB (N=21)	EIB + DB (N=21)	Other (N=12)
Type of exercise-induced symptom	186 (96)	101 (95)	33 (100)	21 (100)	20 (95)	11 (92)
Type of exercise trigger	133 (69)	67 (63)	24 (73)	18 (86)	17 (81)	7 (58)
Localisation of dyspnoea (chest or throat)	92 (48)	37 (33)	25 (76)	10 (48)	13 (62)	7 (58)
Respiration phase (inspiration or expiration)	86 (45)	29 (27)	24 (73)	13 (62)	16 (76)	4 (37)
EIS start (during vs. after exercise)	71 (37)	30 (28)	16 (48)	11 (52)	8 (38)	6 (50)
Inhaled medication for EIS	181 (94)	105 (99)	28 (85)	18 (86)	21 (100)	9 (75)
Effect of Inhaled medication for EIS (n=111*)	98 (88)	62 (86)	12 (86)	8 (100)	13 (93)	3 (100)

Abbreviations: EIB: exercise-induced bronchoconstriction, DB: dysfunctional breathing. *In those who reported yes to use of inhaled medication for EIS

Table 2: Agreement between physician-reported and parent-reported EIS (N=175)

	Physician reported	Parental reported	Agreement between physician-reported and parent reported EIS				Kappa
			physician+ parent +	physician + parent -	physician - parent +	physician - parent -	
Type of symptoms[a] (n=175)							
Wheeze or whistling sounds	56 (32)	101 (57)	43 (25)	13 (7)	58 (33)	61 (35)	0.24
Cough	61 (35)	100 (57)	52 (30)	9 (5)	48 (27)	66 (38)	0.39
Dyspnoea	114 (65)	146 (83)	101 (58)	13 (7)	45 (26)	16 (9)	0.17
Tingling in fingers/lips	2 (1)	31 (18)	2 (1)	0	29 (16)	145 (82)	0.09
Type of exercise-triggers[b] (n=121)							
Running	44 (36)	75 (62)	30 (25)	14 (12)	45 (37)	32 (26)	0.08
Bike	18 (15)	79 (65)	17 (14)	1 (1)	62 (51)	41 (34)	0.14
Intensive sports	81 (67)	94 (78)	63 (52)	18 (15)	31 (26)	9 (7)	0.01
Swimming	8 (7)	46 (38)	8 (7)	0	38 (31)	75 (62)	0.22
Cold weather sports							
Localisation (n=73)							0.36
Chest	40 (55)	41 (56)	*				
Throat	26 (36)	12 (16)					
Chest and Throat	7 (10)	20 (27)					
Respiration phase[c] (n=94)							0.13
Inspiration	47 (50)	47 (50)	*				
Expiration	37 (39)	5 (5)					
Inspiration and Expiration	10 (11)	42 (45)					
EIS start[e] (n=66)							0.19
During exercise	45 (68)	55 (83)	40 (61)	5 (8)	15 (23)	6 (9)	
After ending exercise	21 (32)	11 (17)	6 (9)	15 (23)	5 (8)	40 (61)	
Inhaled medication for EIS[f] (n=159)							0.53
Yes to medication	99 (62)	111 (70)	88 (55)	11 (7)	23 (14)	37 (23)	
Effect of inhaled medication (n=76)							0.27
EIS disappear	23 (30)	17 (22)	*				
EIS reduced	29 (38)	42 (55)					
No difference	24 (32)	17 (22)					

In this table, agreement is described for those where the physician-recorded symptoms was not missing and the parental questionnaire was not missing. [a]PQ:Which symptoms does your child have during exercise? [b]In which of the following situations do the symptoms occur? [c]PQ:If reported dyspnoea: Where is the sensation of symptoms felt the strongest? [d]PQ:When are the symptoms worst? [e]PQ:When do the symptoms begin? [f]PQ:Has your child ever used an asthma-inhaler during EIS? [g]PQ:How well does this asthma-inhaler help? *Cell percentages cannot meaningfully be displayed

Supplementary table 1: Information extracted from outpatient clinic letter and question from questionnaire used to measure agreement with parental reports

Variable	Physician reported EIS, extracted from outpatient clinic letter	Question in questionnaire
Any EIS	Does the child have any exercise-induced symptoms (yes, no, not mentioned)	Does your child sometimes experience breathing problems when exercising? (yes/no)
Wheeze	Expiratory wheeze	Which breathing problems does your child experience when exercising? Wheezing or whistling breathing sounds (yes/no)
Cough	Cough	Which breathing problems does your child experience when exercising? Cough (yes/no)
Dyspnoea	Dyspnoea, shortness of breathing, difficulty breathing	Which breathing problems does your child experience when exercising? Dyspnoea or tightness (yes/no)
Tingling feeling in fingertips or lips	Tingling feeling in fingertips or lips	Does your child sometimes experience a sensation as if ants were creeping around the fingertips or lips while exercising? (yes/no)
Other		Which breathing problems does your child experience when exercising? Other problems (yes/no)
Other, which	Inspiratory stridor, dizziness, fast tired, deep sighing, pain in legs, abnormal sweating, not specified)	If other problems, which? (free text field)
Types of EIS triggers	Which of the following activities trigger exercise-induced symptoms (running, bycycle riding, intensive sport games, swimming, cold weather sports, no exercise triggers specified in letter)	In which of the following situation, does the breathing problems occur? Running short, middle, longer distances, biking, sport games, swimming
Localisation of dyspnoea	Where are the exercise-induced symptoms mainly felt (chest, throat, chest and throat, not specified in letter)	If dyspnoea or tightness, where is the sensation felt the strongest? (Chest, throat, Everywhere (chest and throat))
When are EIS worst	In which respiration phase are the exercise-induced symptoms worst (inspiration, expiration, inspiration and expiration, not specified in letter)	When are the breathing problems worst? (during inspiration, during expiration, equally during inspiration and expiration)
EIS start	When do the exercise-induced symptoms begin (during exercise, after exercise, not specified)	When do the breathing problems begin? – When you child for example runs a longer distance, then the breathing problems normally begin: (straight away after the first steps, a few minutes after beginning the exercise, after ending the exercise)
Inhalation for EIS	Has the child used any inhaled medication before exercise (yes, no, not mentioned)	Has your child inhaled an asthma-spray or asthma-powder for breathing problems occuring when exercising? (yes/no)
Effect of inhalation	How well does the medication help (symptoms disappear, symptoms are reduced, no difference, not mentioned)	If yes: How well does the medication help? (The breathing problems disappear, the breathing problems are reduced, you almost feel no difference)

Supplementary table 2: Population characteristics and diagnosis from outpatient clinic (N=196)

Characteristics	**n(%)**
Age (years) at baseline visit, mean (SD)	12 (3)
Sex (female)	92 (48)
BMI z-score, mean (SD)	0.4 (1.1)
Overweight (BMI z-score >1)	49 (25)
Performs leisure time sports[a]	164 (86)
Swiss nationality	159 (82)
Parental education	
Mother, tertiary[b]	55 (30)
Father, tertiary[b]	75 (41)
Current smoking	
Mother	28 (15)
Father	34 (19)
Respiratory symptoms past 12 months, reported in questionnaire	
Wheeze	105 (54)
>3 attacks of wheeze	58 (30)
Cough at night	72 (37)
Cough more than 2 months	11 (6)
Rhinitis	103 (54)
Any symptoms during exercise	175 (94)
Reason for referral	
Suspected asthma	115 (60)
Suspected inducible laryngeal obstruction	11 (6)
Unknown aetiology	66 (34)
Diagnoses	
Asthma	106 (55)
Extrathoracic DB	33 (17)
Thoracic DB	21 (11)
Asthma plus DB	21 (11)
Other	12 (6)

[a]Apart from schoolsports [b]Degree from university of applied sciences or university

7.5 Publication 5: The Simple 10-item Predicting Asthma Risk in Children Tool to Predict Childhood Asthma – an External Validation

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Original article

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Own contribution: Conceptualise and design study, prepare and analyse data, interpret results, draft manuscript, submit and write point-by-point answer to reviewers.

Original Article

The Simple 10-Item Predicting Asthma Risk in Children Tool to Predict Childhood Asthma—An External Validation

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What is already known about this topic? Several childhood asthma prediction models have been developed, but few have been externally validated.

What does this article add to our knowledge? We found that the simple 10-item Predicting Asthma Risk in Children (PARC) asthma prediction tool performed equally well in a different study population and identified symptomatic preschool children who were likely to have asthma at school age.

How does this study impact current management guidelines? PARC is a simple noninvasive tool for predicting school-age asthma in symptomatic preschool children. It can be used to recruit high-risk children for clinical trials and its use in clinical practice is ready to be tested.

BACKGROUND: External validation of prediction models is important to assess generalizability to other populations than the one used for model development. The Predicting Asthma Risk in Children (PARC) tool, developed in the Leicestershire Respiratory Cohort (LRC), uses information on preschool respiratory symptoms to predict asthma at school age.
OBJECTIVE: We performed an external validation of PARC using the Avon Longitudinal Study of Parents and Children (ALSPAC).
METHODS: We defined inclusion criteria, prediction score items at baseline and asthma at follow-up in ALSPAC to match those used in LRC using information from parent-reported questionnaires. We assessed performance of PARC by calculating sensitivity, specificity, predictive values, likelihood ratios, area under the curve (AUC), Brier score and Nagelkerke's R^2. Sensitivity analyses varied inclusion criteria, scoring items, and outcomes.
RESULTS: The validation population included 2690 children with preschool respiratory symptoms of whom 373 (14%) had asthma at school age. Discriminative performance of PARC was similar in ALSPAC (AUC = 0.77, Brier score 0.13) as in LRC (0.78, 0.22). The score cutoff of 4 showed the highest sum of sensitivity (69%) and specificity (76%) and positive and negative likelihood ratios of 2.87 and 0.41, respectively. Changes to inclusion criteria, scoring items, or outcome definitions barely altered the prediction performance.
CONCLUSIONS: Performing equally well in the validation cohort as in the development cohort, PARC is a valid tool for predicting asthma in population-based cohorts. Its use in clinical practice is ready to be tested. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:943-53)

Key words: *Asthma; Wheeze; Prediction; External validation; PARC; Leicestershire respiratory cohorts; ALSPAC*

Up to 40% of all preschool children have recurrent respiratory symptoms such as wheeze or cough but only about a quarter of these will have asthma at school age.[1-4] Prediction models can be useful to identify those whose problems will persist. The ability to make an accurate prognosis can guide clinical decision making and facilitate the selection of children for high-risk cohorts or clinical trials.[5] Prediction models must be carefully developed using sound methodology for selecting prediction variables and examine discriminative performance and assess calibration.[6]

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Abbreviations used
ALSPAC- Avon Longitudinal Study of Parents And Children
API- Asthma Predictive Index
AUC- Area under the curve
LR- Likelihood ratio
LRC- Leicestershire Respiratory Cohort study
MAS- Multicenter Allergy Study
PARC- Predicting Asthma Risk in Children
PIAMA- Prevalence and Incidence of Asthma and Mite Allergy
ROC- Receiver operator curves

Prediction models may however not perform as well when applied to populations other than the ones they were developed in. External validation (in another population) is therefore necessary to assess the generalizability.[7,8]

Several models to predict later asthma in preschool children have been developed.[9] Most use a combination of demographic information, symptoms, and results of clinical tests (eg, lung function or allergic sensitization).[10-17] These models are useful for specialized clinical settings, where spirometry, body plethysmography, and skin prick test can be performed. Two tools use only demographic information and symptoms; information easily obtained from parental questionnaires or when taking patient history in a medical consultation, which makes these models more widely applicable.[18,19] One of these was developed by our group, the Predicting Asthma Risk in Children (PARC) tool. It was developed using data from the Leicestershire Respiratory Cohorts (LRCs), a population-based cohort study from the United Kingdom.[19] Four childhood asthma prediction models have been externally validated. The Asthma Predictive Index (API)[10] was validated in 5 external cohorts,[11,15,20-22] the Prevalence and Incidence of Asthma and Mite Allergy (PIAMA) risk score[18] was validated in 2 external cohorts,[21,23] the Isle of Wight was validated in 1 external cohort,[24] and the PARC tool was validated in a German asthma cohort, where it showed good predictive properties.[25] However, this was a cohort in which mothers with a history of allergy were overrepresented.

We aimed to validate PARC in a larger population-based cohort in the Avon Longitudinal Study of Parents and Children (ALSPAC). We calculated measures of prediction performance and assessed the robustness of prediction performance to changes in the inclusion criteria, the prediction score items and the outcome.

METHODS

We used the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis guidelines to report this external validation study.[26]

Predicting Asthma Risk in Children

The PARC tool was developed as a simple, low-cost, and noninvasive method to predict the risk of later asthma in symptomatic preschool children.[19] It uses parental information about respiratory symptoms in 1- to 3-year-old children to predict parental reported asthma 5 years later. The 10 scoring factors are sex, age, wheeze without colds, number of wheezing episodes, shortness of breath due to wheeze, wheeze interfering with daily activities, exercise or allergy as triggers of wheeze, a history of eczema, and parental history of asthma and bronchitis. The published model was developed using the least absolute shrinkage and selection operator penalized logistic regression to avoid overfitting and simplified into an easy-to-use tool. We validated the tool internally by using the leave-one-out cross-validation method.[19] The sample size was judged to be sufficient based on the one-variable-per-ten-events rule, which suggests that at least 10 outcome events per potential predictor considered are needed, to develop a model that can generalize to other samples.[8] We considered 38 potential binary predictors (from 24 original variables) and the sample included 345 children with asthma.

Development cohort, LCR

As described previously,[19] the PARC tool was developed using data from the LRC. The LRC is a longitudinal population-based study from Leicestershire, United Kingdom.[27] For the development of PARC, we used data from 6808 children born in 1993-1997. Data for inclusion criteria, prediction score items, and outcomes came from questionnaires on respiratory symptoms and general health that parents completed at baseline in 1998 and 1999 when the children were aged 1-3 years and at follow-up in 2003 when the children were aged 6-8 years. The Leicestershire Health Authority Research Ethics Committee approved the Leicestershire Respiratory Cohort study.

External validation cohort, ALSPAC

In the present study, we used data from the ALSPAC cohort to validate the PARC tool. ALSPAC is a longitudinal birth cohort that recruited 14,541 pregnant women from Avon, United Kingdom, with expected delivery between April 1991 and December 1992, resulting in 14,062 live born children. The study has been described in detail previously.[28] Mothers and their partners filled in questionnaires about their own and their child's health approximately yearly from when the children were 6 months old. We used baseline information from the questionnaires filled in when the child was 1.5, 2.5, and 3.5 years to define inclusion criteria and calculate the prediction score and information from questionnaires completed at age 6 and 7 years to assess asthma at school age. The ALSPAC study was approved by the ALSPAC Ethics and Law Committee and from Local Research Ethics Committees.

Availability of data and material

The LRC dataset is available on reasonable request by contacting Claudia Kuehni. The ALSPAC dataset is available by proposals through the ALSPAC Executive Committee using the procedures outlined in the ALSPAC Access Policy (www.bristol.ac.uk/alspac/researchers/access/).

Inclusion criteria

We defined inclusion criteria for ALSPAC that resembled the inclusion criteria used in the LRC (Table I). We included children aged 1.5 to 3.5 years from ALSPAC who had had wheeze or cough during the past 12 months (Has your child experienced wheeze/cough during the past 12 months?) and saw a doctor for one of these problems (answer category: yes and saw a doctor) plus had valid information on current wheeze and use of asthma medication at age 7.5 years.

Calculation of prediction scores

Items used for the prediction score are presented in Table II for LRC and ALSPAC. In ALSPAC, the same questionnaires were sent to the parents at 1.5, 2.5, and 3.5 years of age. To achieve a comparable age distribution in ALSPAC as in the LRC, the baseline information was taken from the questionnaire filled at age 1.5 years

TABLE I. Inclusion criteria and outcome definitions in LRC and ALSPAC

LRC: items for inclusion criteria* (at age 1-3 y)	Answer categories	ALSPAC: items for inclusion criteria* (at age 0.5, 1.5, 2.5 y)	Answer categories	Comparability
Has your child had wheezing or whistling in the chest in the last 12 mo?	Yes, no	Has he had any of the following the last 12 mo, wheezing?	Yes and saw a doctor	Good
			Yes but did not see a doctor	
			No did not have	
Does your child usually have a cough without colds?	Yes, no	Has he had any of the following the last 12 mo, cough?	Yes and saw a doctor	Moderate
			Yes but did not see a doctor	
			No did not have	
In the last 12 mo, has your child had a dry cough at night, apart from a cough associated with a cold or a chest infection?	Yes, no	No question	–	–
How often did your child see a GP for coughing or wheezing during the last 12 mo?	Never, once, 2-3 times, 4-6 times, 7 or more times	Has he had any of the following the last 12 mo, wheezing?	Yes and saw a doctor	Good
			Yes but did not see a doctor	
			No did not have	
In the last 12 mo, has wheezing or asthma resulted in your child: (4 categories: referred/admitted to hospital, attending/calling ER or GP)	Yes, no	No question	–	–
LRC: items for outcome definition† (at 8 y)	**Answer categories**	**ALSPAC: items for outcome definition† (at 7.5 y)**	**Answer categories**	**Comparability**
Has your child had wheezing or whistling in the chest in the last 12 mo?	Yes, no	Has he had any of the following in the past 12 mo, wheezing?	Yes and saw a doctor	Very good
			Yes but did not see a doctor	
			No did not have	
Did your child take any of the following during the last 12 mo? (4 categories: inhalers by content/type)	Yes, no, don't know	Please indicate which of the following have been given to your child the last 12 mo. Asthma medication?	Never	Very good
			Yes for 1-2 episodes only	
			Yes for 3 or more episodes	

ALSPAC, Avon Longitudinal Study of Parents and Children; *ER*, emergency room; *GP*, general practitioner; *LRC*, Leicestershire Respiratory Cohort.
*Inclusion criteria LRC: wheeze or cough (cough without colds or cough at night) with 1 or more visits to the doctor for wheeze or cough during the past 12 mo). Inclusion criteria ALSPAC: wheeze or cough during the past 12 mo and saw a doctor for one of these problems (answer category: yes and saw a doctor).
†Outcome definition LRC: "Yes" to wheeze and use of asthma medication past 12 mo. Outcome definition ALSPAC: "Yes" to wheeze and use of asthma medication past 12 mo.

for 28% of the study population, at age 2.5 years for 57%, and at age 3.5 for 15%. The age at which baseline information was taken for a given child was obtained by random sampling ensuring this overall age distribution. Information on parental history of wheeze, asthma, and bronchitis came from a questionnaire sent to the mother at 12 weeks of gestation and from a questionnaire sent to the partner when the child was 33 months old. The prediction score was calculated as the sum of score points from each item (Table II). We also assigned predicted probabilities for later asthma to these scores as suggested in our report on the development of PARC.[19]

Definition of outcome

In the original cohort, we had defined the outcome "asthma" as "current wheeze plus use of asthma inhalers in the past 12 months." To match this outcome definition in ALSPAC, we defined "asthma" as "yes" to the parent-reported current wheeze ("Has he/she had wheeze in the past 12 months") plus current use of asthma medication ("Please indicate which of the following have been given to your child in the last 12 months? Asthma medication").

Assessing predictive performance

We assessed how well the calculated PARC prediction scores predicted later asthma in children from the ASLPAC cohort using measures of discrimination (the ability of the score to discriminate between children who had asthma at school age and those who had not) and calibration (the ability of the tool to predict the probability of later asthma).[8] To assess discrimination, we calculated sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios (LRs) for each possible cutoff value of the score. We also plotted receiver operator curves (ROC)

TABLE II. Questionnaire items used for scoring and their distribution in LRC and ALSPAC

Item no.	Question item in LRC	Score value	(%)	Questionnaire item in ALSPAC	Score value	(%)	Comparability
1	What is the child's sex	Female = 0	(45)	Sex	Female = 0	(47)	Perfect
		Male = 1	(55)		Male = 1	(53)	
2	How old is the child?	1 y = 0	(27)	Age	1 y = 0	(28)	Perfect
		2 y = 1	(57)		2 y = 1	(57)	
		3 y = 1	(15)		3 y = 1	(15)	
3	In the last 12 mo, has the child had wheezing or whistling in the chest even without having a cold or flu?	No = 0	(82)	Because she was 6/18/30* mo old, has she had any periods when there was wheezing with whistling on her chest when she breathed?	No = 0	(71)	Moderate. Question does not include "without cold"
		Yes = 1	(18)		Yes = 1	(29)	
4	How many attacks of wheeze has the child had during the last 12 mo?	0-3 = 0	(77)	Has your baby ever had wheezing with whistling on her chest when she breathed?	0-3 = 0	(82)	Very good
		>3 = 2	(23)	How many separate times has this happened	>3 = 2	(18)	
5	In the last 12 mo, how much did wheezing interfere with your child's daily activities?	Never = 0	(64)	Proxy: "how many days altogether would you say he had wheezed in the past 12 mo?"	0-3 d = 0	(77)	Poor. Different question.
		A little = 1	(26)		4-19 d = 1	(16)	
		A lot = 2	(10)		20 or more days = 2	(7)	
6	Do these wheezing attacks cause him/her to be short of breath?	Never = 0	(65)	Because she was 6/18/30* mo old, has she had any periods when there was wheezing with whistling on her chest when she breathed?	No for all = 0	(84)	Very good
		Sometimes = 2	(29)	Was he breathless (struggling for breath) during any of these times?	Yes for some = 2	(15)	
		Always = 3	(6)		Yes for all = 3	(1)	
7	In the last 12 mo, did exercise (playing, running) or laughing, crying, or excitement cause wheezing or coughing in the child?	No = 0	(61)	Has your baby ever had wheezing with whistling on her chest when she breathed?	No = 0	(99)	Moderate. Optional free text field—few answers
		Yes = 1	(39)	What do you think brings them on? (exercise, emotion)	Yes = 1	(1)	
8	In the last 12 mo, did contact with dust, grass, pets or other animals cause wheezing or coughing in the child?	No = 0	(93)	Has your baby ever had wheezing with whistling on her chest when she breathed?	No = 0	(99)	Moderate. Optional free text field—few answers
		Yes = 1	(7)	What do you think brings them on? (allergy)	Yes = 1	(1)	

9	Has the child ever had eczema?	No = 0	(57)	Has the baby had a rash in the joints and creases of her body (eg, behind the knees, under the arms)?	No = 0	(71)	Good. Asking about rash instead of eczema	
		Yes = 1	(43)		Yes = 1	(29)		
10	Has the child's parents ever suffered from wheezing, asthma, or bronchitis?	None = 0	(52)	Have you ever had any of the following problems: asthma/ wheezing past 2 y	None = 0	(65)	Moderate. Information asked from partner instead of father	
		Mother = 1	(17)	Have you had wheeze or bronchitis since the child was born (8 mo after birth)	Mother or father = 1			
		Father = 1	(22)		Both = 1	(31)		
		Both = 1	(9)			(4)		

ALSPAC, Avon Longitudinal Study of Parents and Children; *LRC*, Leicestershire Respiratory Cohort.
*Ages correspond to age 12 mo before questionnaire mailing.

and calculated area under the curve (AUC). To assess calibration, we assigned the probabilities of later asthma to each score value as proposed in the original article by Pescatore et al.[19] On the basis of these predicted probabilities, we first calculated the maximum rescaled Brier score and Nagelkerke's R^2 as overall performance measures.[8] These measures can be interpreted as "goodness-of-fit measures" showing how well the predicted probability approximates the outcome on a scale between 0 and 1, with 1 indicating perfect prediction and 0 representing a noninformative model, in which a constant probability equaling the prevalence of the outcome is predicted for each child. Details on how to compute these measures are provided in this article's Online Repository at www.jaci-inpractice.org. We examined calibration of the PARC tool graphically by plotting the predicted probability for each value of the score against the observed frequency of asthma among ALSPAC children with that score value, using the function calibrate.plot and val.prob.ci.2 from the "gbm" package in R (R Foundation, Vienna, Austria).[29] We excluded children if they had missing information in any of the scoring variables (8%) apart from the item "partner's history of wheeze, asthma, and bronchitis," for which 25% had missing information. For these children, we set missing information about the partner to "no history."

In a separate analysis, we recalibrated the PARC scores in the ALSPAC cohort, by fitting a logistic regression of the outcome on the calculated scores (as a linear term) used in the main analysis above. For each child, we then calculated recalibrated scores as the value of the linear predictor from this regression. We then compared calibration performance of these scores with that of the original scores.

We used STATA 14 for data preparation and descriptive analysis and R version 2.1 to study model performance and model fit.

Sensitivity analyses

To test the robustness of PARC, we performed sensitivity analyses in ALSPAC and LRC datasets using alternative definitions of the included population, prediction score items, and outcome definitions (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). First, we restricted age at baseline by including children aged 1.5, 2.5, and 3.5 years only (only ALSPAC). Secondly, we altered the inclusion criteria to: (1) any wheeze in the past 12 months, and (2) any cough in the past 12 months (only in ALSPAC). Thirdly, we changed items in the prediction score by: (1) excluding "wheeze triggered by exercise or allergy," as triggers of wheeze were measured differently in ALSPAC (open question) compared with LRC (specific response categories), and (2) exchanging "wheeze without colds" with "current wheeze" (only in LRC), (3) setting missing information in the prediction score items to the lowest value instead of excluding children with missing values in the analysis. Fourthly, we used an alternative outcome definition: severe asthma (ALSPAC: current wheeze and use of asthma medication on at least 3 episodes, LRC: wheeze on at least 4 episodes and use of asthma inhalers).

Sample size

There are no guidelines for the adequate sample size needed for external validations of the prediction model, but according to a simulation study by Collins et al,[30] ideally 200 events are required. We had more than 300 events (asthma at age 7.5 years) in any of our analyses.

TABLE III. Comparison of study characteristics and demographic factors in development cohort (LRC) and external validation cohort (ALSPAC)

Variable	Development cohort (LRC) N = 1226	Validation cohort (ALSPAC) N = 2690
Location	Leicestershire (United Kingdom)	Bristol (United Kingdom)
Study design	Prospective cohort (from birth)	Prospective cohort (from pregnancy)
Recruitment	General population random sample	General population random sample
Year of birth	1995-1997	1991-1992
Sex		
Male	678 (55)	1433 (54)
Ethnicity		
White	797 (69)	2580 (98)
South Asian	305 (26)	–
Other	57 (5)	52 (2)
Baseline assessment		
Age*		
1 y	336 (27)	763 (28)
2 y	702 (57)	1516 (56)
3 y	188 (15)	411 (15)
Wheeze† prevalence	766 (62)	791 (29)
Cough† prevalence	1085 (89)	2654 (99)
Follow-up assessment		
Age		
6 y	336 (27)	
7 y	702 (57)	2690 (100)
8 y	188 (15)	
Wheeze† prevalence	427 (35)	451 (17)
Use of asthma medication†	345 (28)	586 (22)
Wheeze† + use of asthma medication†	345 (28)	373 (14)

ALSPAC, Avon Longitudinal Study of Parents and Children; *LRC*, Leicestershire Respiratory Cohort.
This table is displayed using n (%) unless otherwise stated.
*The age distribution at baseline in ALSPAC was matched to the baseline age distribution in LRC.
†In the past 12 months. Prevalence of wheeze and cough is so high, because only children with lower respiratory symptoms were included.

RESULTS

Of the 14,541 children originally recruited in ALSPAC, 7200 children responded to the questionnaires at 1, 2, 3, and 7 years. Of these, 2921 fulfilled the inclusion criteria (saw a doctor for wheeze or cough in the past 12 months) and 2690 were included in our main analysis (231 were excluded because of missing information in 1 or more prediction score items). Not all questions used to specify inclusion criteria in the LRC were available in ALSPAC resulting in less restrictive inclusion criteria (Table I). Table III shows similarities and differences between the 2 studies including location in the United Kingdom and the gender and age distribution. The 2 cohorts differed considerably in ethnicity composition (98% whites in ALSPAC, 81% whites, and 19% south Asians in LRC).

Distribution of the PARC score

For most items of PARC, we were able to use similar questions in ALSPAC as in the LRC (Table II). There were some differences for "wheeze without colds," questions on triggers for wheeze, and parental history of wheeze and bronchitis. Assigning scores to ALSPAC children resulted in a more left skewed distribution of the PARC score in ALSPAC compared with the LRC (Figure 1). The maximum and median values were lower in the ALSPAC cohort (max = 13, median = 2, interquartile range: 2-4) compared with the LRC cohort (max = 14, median = 4, interquartile range: 2-6).

Frequency of asthma at follow-up

In ALSPAC, 373 (14%) of the included children had the primary outcome at age 7.5 years compared with 345 (28%) in LRC (Table III).

Performance of PARC main analysis

The discriminative ability of PARC was similar in ALSPAC and LRC (Figure 2). ROC curves from ALSPAC and LRC were almost identical, AUC of 0.77 in ALSPAC and 0.78 in LRC. In ALSPAC, the score cutoff maximizing the sum of sensitivity (69%) and specificity (76%) was 4, and in LRC, the best cutoff was 5 (sensitivity 72%, specificity 71%). The validation analysis showed positive and negative predictive values of 0.32 and 0.94 and positive and negative LRs of 2.87 and 0.41, respectively, all at the score cutoff 4 (discriminative values for all cutoff points in Figure 2). Overall performance in ALSPAC was comparable with that in LRC. The max-scaled Brier score was 0.13 in ALSPAC and 0.22 in LRC, and Nagelkerke's R^2 was 0.23 in ALSPAC and 0.28 in LRC. The calibration assessment showed that PARC scores from the ALSPAC population were associated with a lower frequency of later asthma than predicted from the LRC (Figures 3 and 4). After recalibrating the predicted probabilities

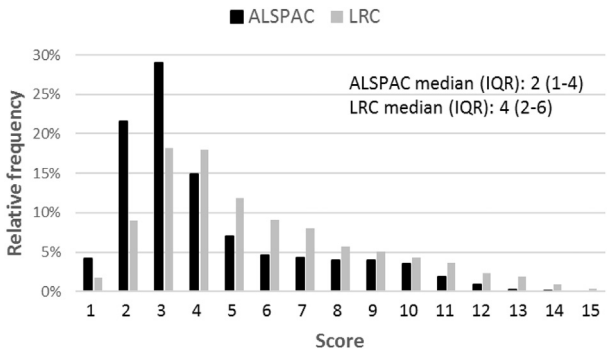
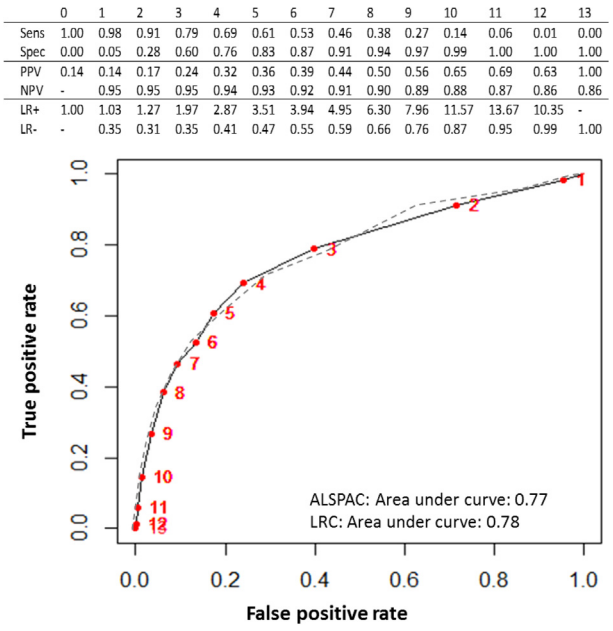


FIGURE 1. *Score based on items described in table 3 for ALSPAC and LRC, respectively. Distribution of the PARC scores* (relative frequency) in the external validation population (ALSPAC, n = 2690, black) and original development population (LRC, n = 1226, grey). *ALSPAC*, Avon Longitudinal Study of Parents and Children; *IQR*, Interquartile range; *LRC*, Leicestershire Respiratory Cohort; *PARC*, Predicting Asthma Risk in Children.



	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Sens	1.00	0.98	0.91	0.79	0.69	0.61	0.53	0.46	0.38	0.27	0.14	0.06	0.01	0.00
Spec	0.00	0.05	0.28	0.60	0.76	0.83	0.87	0.91	0.94	0.97	0.99	1.00	1.00	1.00
PPV	0.14	0.14	0.17	0.24	0.32	0.36	0.39	0.44	0.50	0.56	0.65	0.69	0.63	1.00
NPV	-	0.95	0.95	0.95	0.94	0.93	0.92	0.91	0.90	0.89	0.88	0.87	0.86	0.86
LR+	1.00	1.03	1.27	1.97	2.87	3.51	3.94	4.95	6.30	7.96	11.57	13.67	10.35	-
LR-	-	0.35	0.31	0.35	0.41	0.47	0.55	0.59	0.66	0.76	0.87	0.95	0.99	1.00

FIGURE 2. Receiver operating characteristic from validation population ALSPAC (solid line) and the original development population LRC (dashed line). Numbers (1-13) indicate asthma prediction score values and their corresponding positions (indicated in red in the figure). The area under the curve corresponds to the primary outcome in both cohorts. The table above the figure shows sensitivity (Sens), specificity (Spec), positive and negative predictive values (PPV, NPV) and likelihood ratios (LR+, LR−) for each score point in ALSPAC. *ALSPAC*, Avon Longitudinal Study of Parents And Children; *LRC*, Leicestershire Respiratory Cohort.

in ALSPAC (Figure 4, *B*), our calibration plot showed good calibration of PARC in ALSPAC (Brier score = 0.17 for the recalibrated main model).

Sensitivity analyses

Changes in inclusion criteria, prediction score items, and definition of outcome resulted only in minor changes for most performance measures (Table IV). In sensitivity analyses, PARC performed better in children aged 3.5 years (AUC = 0.78, R^2 = 0.26), compared with 1.5-year-olds (AUC = 0.71, R^2 = 0.13). Prediction was slightly worse in a population including only children who wheezed (AUC = 0.73, R^2 = 0.18) compared with those who also saw a doctor or only children who coughed with or without seeing a doctor (AUC = 0.76, R^2 = 0.20). The exclusion of trigger variables in ALSPAC barely altered the performance. PARC performed better when the main outcome was severe asthma (AUC = 0.78, R^2 = 0.23). Sensitivity analysis where results excluding missing information were compared with results where missing information was set to zero showed no difference in the performance of PARC (data not shown).

DISCUSSION

We found that PARC predicted asthma at school age equally well in the validation cohort, ALSPAC (AUC 0.77), compared with the development cohort, LRC (AUC 0.78). Using a cutoff score value of 4, PARC predicted asthma with a sensitivity of 69% and specificity of 76%, which was similar to what was found in LRC for a cutoff score of 5 (sensitivity = 72% and specificity = 71%). The calibration assessment showed that the observed frequency of asthma was generally lower in ALSPAC than predicted by the PARC score, but when we recalibrated the predicted probabilities to the ALSPAC population, agreement between predicted and observed asthma frequency was good.

Limitations and strengths

The information used to define the included population was not the same in ALSPAC as in LRC. Specifically, the ALSPAC cohort had insufficient information on night cough and cough without colds, so we replaced this information with a general question about cough. These relaxed inclusion criteria have led to the inclusion of less severely affected children than the LRC population, which in turn explains the lower prevalence of asthma at school age (14% in ALSPAC compared with 28% in LRC). This did not affect the discriminative ability of PARC, but it affected calibration and the overall performance measures such as the Brier score. Furthermore, we lacked perfectly matched information on items needed to compute the PARC score. Key information for the score such as wheeze without colds and triggers of wheeze were not available in the same detail. However, our sensitivity analysis in ALSPAC suggested that exclusion of triggers of wheeze did not affect the performance much (AUC 0.77, same as the main analysis).

A strength of our study was that we had full access to all data from the development and the validation cohort, which made it possible to compare the populations and assess discriminative performance and calibration of PARC directly. Secondly, the cohort used for the external validation was large and had collected questionnaire information yearly between birth and the age of 8 years. This enabled us to match and vary the age at which baseline and outcome information was collected. Thirdly, less than 5% of the information in the single variables used for scoring (apart from the partner's history of asthma and wheeze) was missing and we therefore excluded only a small number of the children satisfying the inclusion criteria (8%). Sensitivity analysis, in which missing information was set to zero, did not

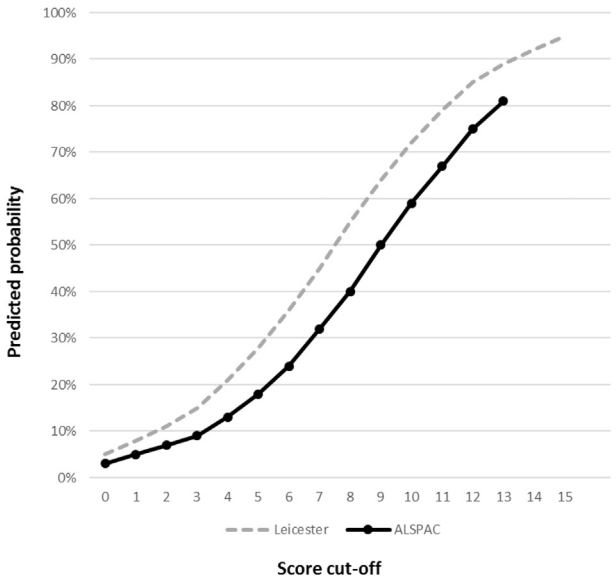


FIGURE 3. Predicted probability of developing asthma at follow-up in LRC (dashed gray line) and probabilities predicted by the recalibrated model in ALSPAC (black line). *ALSPAC*, Avon Longitudinal Study of Parents And Children; *LRC*, Leicestershire Respiratory Cohort.

change our main results. Fourthly, for the primary outcome, we had a perfect matching on current wheeze and use of asthma medication at the age of 7.5 years, and we could therefore rule out that differences in performance of the PARC tool in ALSPAC and LRC cohorts were caused by different outcome definitions.

Comparison with other studies

One other study has investigated the external validity of PARC and found similar performance to the original cohort.[25] The study used information from the German Multicenter Allergy Study (MAS-90) birth cohort with an overrepresentation of children from allergic parents. The authors included 140 children in their validation population. The authors found that PARC predicted asthma with AUC = 0.83 and a sensitivity of 0.82 and a specificity of 0.69 at a score of 5. The calibration assessment showed good agreement between predicted probabilities of asthma and observed frequency.

Of the other models developed to predict asthma in children, 3 have been externally validated (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). The API developed using the Tucson Children's Respiratory Study in 2000[10] was externally validated in 5 separate studies,[11,15,20-22] showing generally higher sensitivity, but lower specificity than in the development cohort, which could partly be explained by differences in inclusion criteria. Caudri et al[18] developed an asthma prediction model using the PIAMA,[18] which was externally validated in a Columbian clinical cohort of children with wheeze[21] and in the Dutch population-based Generation R study[23] and showed similar performance to the development cohort. The calibration assessment showed that the PIAMA risk score systematically overestimated asthma risk at age 7 years. Kurukulaaratchy et al[13] developed a prediction model in the Isle of Wight birth cohort, which was applied in the British MAS birth cohort, where calibration showed different predictive properties from the development cohort. The evidence from these external validation studies and the present study suggests that these prediction models are generally robust in different populations and discriminate asthma from no asthma well in different settings, but calibration must be assessed for the models to accurately predict asthma risk. Among the existing prediction models that have been externally validated, PARC and the PIAMA risk score are the models most easily applied in practice as they require no specific physiological measurements or blood investigations as does, for example, the API (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). In addition, PARC predicts as well or better than other existing asthma prediction tools when comparing the combined sensitivity and specificity using the Youden index[31] (sensitivity + specificity − 1, calculated based on the maximal sum of sensitivity and specificity), which ranges from 0 to 1, with 1 indicating perfect prediction. The reported values of the Youden index are 0.43 for PARC compared with 0.32 for the API, 0.36 for the PIAMA risk score, and 0.38 for the Isle of Wight score.[19] PARC has a similar positive LR (true positives/false positives) (+LR = 2.5) to the PIAMA risk score (+LR = 2.5) but lower than the API (+LR = 7.8) and the Isle of Wight (+LR = 3.4) (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). These differences could be due to different inclusion criteria used for the study populations in which the prediction scores were developed. The API was developed in a general population sample including mostly healthy children. Such a population has a low baseline risk of asthma at follow-up, whereas the populations used for PARC and the PIAMA score included only children visiting doctors for wheeze or chronic cough who thus had a higher baseline risk of asthma at follow-up. In a population with low baseline risk, it may be easier to correctly identify those who will not develop asthma, which increases specificity and, assuming the same sensitivity, increases the positive LR. Also, the positive LR can be interpreted as the ratio of posterior odds (after a model predicts that a child will have asthma based on baseline information) of having later asthma to the prior odds (ignoring baseline information). A higher positive LR is needed to achieve the same posterior likelihood of asthma if the baseline risk is low compared with when it is high.

Interpretation

PARC predicted asthma better in children who were older at the baseline survey. A reason for this could be that the etiology of wheeze in children aged less than 2 years is more heterogeneous and only a small proportion will eventually have asthma. In a study using data from ALSPAC, Henderson et al[32] investigated wheezing phenotypes over time and found a majority of children with the phenotype transient early wheeze begin wheezing in the first 2 years of life. In our data, we saw that more children fulfilled our inclusion criteria early in life (3583 1.5-year-olds compared with 2238 3.5-year-olds), but the proportion of children who had asthma at school age was lower among children aged 1.5 years initially (12%) than in children aged 3.5 years at baseline (19%). This may explain the poorer prediction, particularly poorer calibration, among 1.5-year-olds.

The different phenotypes of wheeze might also explain why the predictive performance of PARC was better for severe asthma. Several studies have identified a phenotype characterized by persistence of symptoms from an early age.[3,32,33] Children with

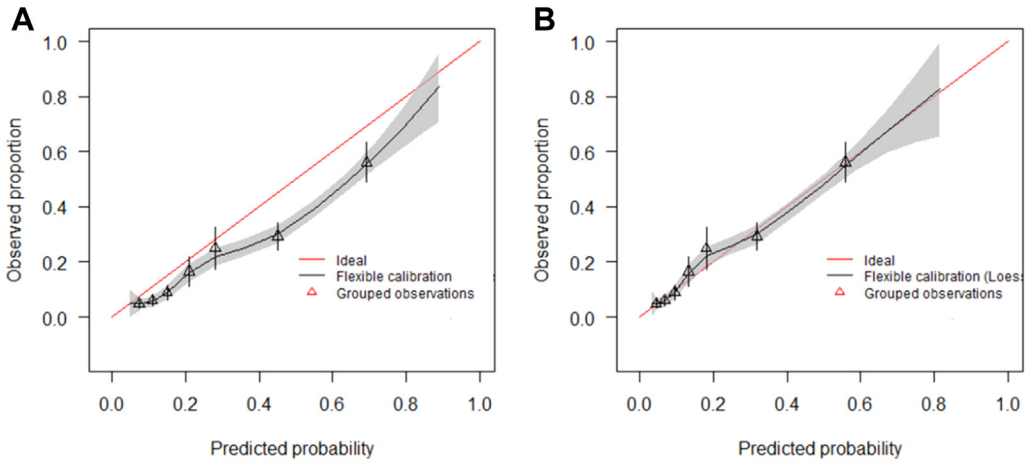


FIGURE 4. Calibration assessment of predicted probabilities versus observed asthma frequencies in 7 equally sized groups. **A**, The calibration assessment for the predicted probabilities calculated in LRC. **B**, The probabilities predicted by the recalibrated model in ALSPAC. The shaded areas represent exact pointwise 95% CI for asthma frequency. The diagonal red line represents perfect calibration. *ALSPAC*, Avon Longitudinal Study of Parents And Children; *CI*, confidence interval; *LRC*, Leicestershire Respiratory Cohort.

TABLE IV. Predictive performance of PARC for main analysis and sensitivity analyses in ALSPAC and LRC (definitions of main and sensitivity analyses in Table E1, available in this article's Online Repository at www.jaci-inpractice.org)

		N	Cases (%)	Sens	Spec	PPV	NPV	LR+	LR−	AUC	R^2	Brier score
	ALSPAC											
A1	Main analysis	2690	373 (14)	0.69	0.76	0.32	0.94	2.87	0.41	0.77	0.23	0.13
A2	Altered inclusion criteria											
A2.1	Only children aged 1 y	3583	439 (12)	0.51	0.80	0.26	0.92	2.53	0.61	0.71	0.13	0.06
A2.2	Only children aged 2 y	2817	410 (14)	0.69	0.72	0.29	0.93	2.42	0.44	0.76	0.21	0.07
A2.3	Only children aged 3 y	2238	396 (19)	0.62	0.82	0.43	0.91	3.46	0.46	0.78	0.26	0.21
A2.4	Wheeze past 12 mo	1423	326 (23)	0.81	0.46	0.31	0.89	1.49	0.42	0.73	0.18	0.08
A2.5	Cough past 12 mo	6351	554 (9)	0.52	0.87	0.28	0.95	4.11	0.55	0.76	0.20	0.07
A3	Altered scoring variables											
A3.1	Exclude trigger variables	2690	373 (14)	0.69	0.76	0.32	0.94	2.89	0.41	0.77	0.23	0.13
A4	Altered outcome definition											
A4.1	Severity: wheeze past 12 mo and use of asthma medication at 3 or more episodes	2688	307 (11)	0.70	0.75	0.26	0.95	2.78	0.40	0.78	0.23	0.06
	LRC											
L1	Main analysis	1226	345 (28)	0.79	0.57	0.42	0.87	1.83	0.38	0.78	0.28	0.22
L2	Altered inclusion criteria											
L2.1	Wheeze past 12 mo	1033	330 (32)	0.72	0.53	0.42	0.80	1.52	0.53	0.69	0.17	0.14
L3	Altered scoring variables											
L3.1	Exclude trigger variables	1226	345 (28)	0.74	0.63	0.44	0.86	2.04	0.40	0.77	0.28	0.22
L3.2	Exchange wheeze without colds with current wheeze	1226	345 (28)	0.82	0.53	0.40	0.88	1.73	0.34	0.77	0.28	0.21
L4	Altered outcome definition											
L4.1	Severity: wheeze past 12 mo more than 4 episodes and use of asthma medication	1030	86 (8)	0.86	0.61	0.17	0.98	2.19	0.23	0.84	0.32	−0.15*

ALSPAC, Avon Longitudinal Study of Parents and Children; *AUC*, area under the curve; *LR*, negative likelihood ratio; *LR+*, positive likelihood ratio; *LRC*, Leicestershire Respiratory Cohort; *NPV*, negative predictive value; *PARC*, Predicting Asthma Risk in Children; *PPV*, positive predictive value; R^2, Nagelkerke's; *Sens*, sensitivity; *Spec*, specificity.

Sens, Spec, PPV, NPV, LR+, LR− are all presented for the PARC score = 4.

*The negative scaled Brier score is due to the large difference in the prevalence of the outcome in main analysis and the corresponding sensitivity analysis.

this phenotype tend to have more wheezing episodes, more often use bronchodilators, and cough without colds compared with wheeze phenotypes with late onset transient or viral wheeze. Because severity tends to track,[34] PARC identifies those with more severe disease at school age because these children often had already severe symptoms early in life. As disease burden is greater in children with severe asthma, they are the main target group for interventions.

The discriminative ability of PARC appears robust to changes in item and population definitions. Although different questions were used in the 2 cohorts, they probably measure similar concepts. This makes PARC useful also in settings with misclassification of information. Outcome prevalence appears to be the more critical factors affecting predictive performance. Therefore, if PARC is to be used in a population with outcome prevalence very different from that in LRC, we recommend simple recalibration of PARC, which allows obtaining risk probabilities that are closer to the observed frequencies. Practically, one approach for calibration could be to examine the prevalence of school-age asthma in the population in question and compare it with LRC or ALSPAC. If the observed frequencies are similar to those in LRC or ALSPAC, the predicted probabilities calculated in the original study or this validation study can be used. If the prevalence is much higher or much lower, it might be necessary to collect (possibly retrospectively from medical records) information from a subsample of children to fill in the PARC tool and thereby calculate new predicted probabilities.

The ALSPAC cohort did not offer the possibility of validating the PARC tool in different ethnic groups as the ALSPAC included 98% whites. The PARC tool would need to be externally validated in a sample with a larger ethnic diversity to determine the generalizability of PARC in different ethnic settings.

The sample size in the original development of the PARC prediction model was estimated to be sufficient according to the one-variable-per-ten-events rule with 24 potential predictor variables (represented by 38 binary variables) and 345 events.[35] However, the appropriateness of this rule has been questioned.[36] It is possible that our original study did not have sufficient statistical power to identify some important predictors among the 38 predictors considered, although 10 of these were retained in the final model and are used in the PARC tool. That the PARC tool includes irrelevant predictors as a result of overfitting is less likely as we used penalized logistic regression to build the tool. Furthermore, almost all predictors included in PARC are either recognized risk factors (male sex, parental history) or are indicators of atopy or symptom severity, which are both known to be associated with persistence. The only exception is older age ($\geq$1 year), which is a plausible predictor, as wheeze or cough in infancy is more transient and usually associated with respiratory infections.

CONCLUSIONS

This validation study showed that PARC has the same ability to identify preschool children who are likely to develop asthma at 7.5 years in a population different from the development cohort. The discriminative ability of the tool appears to be robust to changes in inclusion criteria, scoring variables, and outcome definitions suggesting that PARC is robust to misclassification of information. Our study suggests that the tool may need recalibration when applied to populations, in which the outcome prevalence differs greatly from the development cohort. PARC is a valid tool for predicting asthma in preschool children and its use in clinical practice is ready to be tested.

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E. S. L. Pedersen, B. D. Spycher, and C. E. Kuehni made substantial contributions to the study conception and design and were involved in the drafting of the manuscript. A. Ramette contributed to the study management and data preparation. E. S. L. Pedersen, B. D. Spycher, and F. Halbeisen were responsible for the statistical analyses. A. J. Henderson and R. Granell were involved in data collection and preparation of Avon Longitudinal Study of Parents and Children. E. S. L. Pedersen, B. D. Spycher, F. Halbeisen, C. de Jong, A. Ramette, E. A. Gaillard, A. J. Henderson, R. Granell, and C. E. Kuehni critically revised and approved the manuscript.

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ONLINE REPOSITORY

Definition of the Scaled Brier Score and Nagelkerke's R^2

In the following, let y_i represent the outcome for child i taking on the value 1 if the child has later asthma and 0 otherwise, and p_i the predicted probability based on the baseline information of that child using the Predicting Asthma Risk in Children (PARC) tool. Let n be the total number of children in the cohort and $\bar{y} = \frac{1}{n}\sum_{i=1}^{n} y_i$ be the prevalence of the outcome.

Scaled Brier Score

The Brier score evaluates the mean squared error of prediction[E1]:

$$\text{Brier} = \frac{1}{n}\sum_{i=1}^{n}\left(p_i - y_i\right)^2$$

This score takes on the minimum value of 0 when p_i predicts y_i perfectly. To obtain a similar interpretation for this statistic as for R^2 in linear regression models, we rescale this score as

$$\text{Brier}_{\text{scaled}} = 1 - \frac{\text{Brier}}{\text{Brier}_{\text{max}}}$$

where $\text{Brier}_{\text{max}}$ is the Brier score evaluated with $\bar{y}$ replacing p_i in the formula above. $\text{Brier}_{\text{scaled}}$ takes on values between 0 and 1 with 1 representing perfect prediction and 0 a noninformative prediction model in which the outcome for each child is predicted with a constant equal to the prevalence $\bar{y}$.

Nagelkerke's R^2

Nagelkerke's R^2 compares the likelihood of the prediction model with that of a noninformative model in which the outcome for each child is predicted with a constant equal to the prevalence $\bar{y}$. It is calculated as follows:[E1,E2]

$$R^2_{\text{NK}} = \frac{1 - \left(L_0/L_1\right)^{2/n}}{1 - \left(L_0\right)^{2/n}}$$

where L_1 and L_0 are the likelihood of PARC and the noninformative models, respectively. The denominator of this equation is simply used for rescaling and represents the maximum value that the numerator can attain (in a perfect model $L_1 = 1$). As $\text{Brier}_{\text{scaled}}$, the statistic R^2_{NK} thus takes on values between 0 and 1 with 1 representing perfect prediction and 0 the noninformative model. The likelihood function evaluated for the predictions of the PARC tool is given by

$$L_1 = \prod_{i-1}^{n} p_1^{y_i}\left(1 - p_i\right)^{\left(1-y_i\right)}$$

L_0 is calculated by replacing p_i with $\bar{y}$ in this formula.

TABLE E1. Overview of the definitions of main analysis and sensitivity analyses in ALSPAC and LRC.

	Analysis	Definition changed	Definition
	ALSPAC		
A1	Main analysis	–	Inclusion criteria: wheeze or cough in the past 12 mo and saw a doctor for this. Scoring variables: (1) sex, (2) age, (3) wheeze past 12 mo, (4) number of wheeze attacks, (5) number of days wheezed, (6) breathless due to wheeze, (7) exercise as trigger for wheeze, (8) allergy as trigger for wheeze, (9) rash in the joints, and (10) family history of asthma or bronchitis. Outcome definition: wheeze past 12 mo and use of asthma medication
A2	Altered inclusion criteria		
A2.1	Only children aged 1 y	Inclusion criteria	Age excluded as a prediction variable
A2.2	Only children aged 2 y	Inclusion criteria	Age excluded as a prediction variable
A2.3	Only children aged 3 y	Inclusion criteria	Age excluded as a prediction variable
A2.4	Wheeze past 12 mo	Inclusion criteria	Past 12 mo: "Has he/she had periods when there was wheezing with whistling on his/her chest?" or "Has he/she had wheeze?"
A2.5	Cough past 12 mo	Inclusion criteria	Past 12 mo: "Has he/she ever had a time when he has coughed on and off for at least 2 d?" or "Has he/she had cough?"
A3	Altered scoring variables		
A3.1	Exclude trigger variables	Scoring variables	Exclude items 7 and 8: exercise and allergy as triggers for wheeze
A4	Altered outcome definition		
A4.1	Severity: wheeze past 12 mo and use of asthma medication at 3 or more episodes	Outcome	"Has he had wheeze in the past 12 mo?" and "Please indicate which of the following have been given to your child in the past 12 mo" (answer category: asthma medication, on 3 or more episodes)
	LRC		
L1	Main analysis	–	Inclusion criteria: wheeze or cough apart from colds in the past 12 mo and saw a doctor for wheeze or cough. Scoring variables: (1) sex, (2) age, (3) wheeze apart from colds, (4) number of wheeze attacks, (5) wheeze interference with daily life, (6) shortness of breath due to wheeze, (7) exercise or emotion as trigger for wheeze, (8) allergy as trigger for wheeze, (9) child ever had eczema, and (10) family history of wheeze, asthma, or bronchitis. Outcome: wheezing or whistling in the chest in the last 12 mo, and use of asthma medication
L2	Altered inclusion criteria		
L2.1	Wheeze past 12 mo	Inclusion criteria	"Has your child has wheezing or whistling in the chest in the last 12 mo?"
L3	Altered scoring variables		
L3.1	Exclude trigger variables	Scoring variables	Exclude items 7 and 8: exercise and allergy as triggers for wheeze
L3.2	Exchange wheeze without colds with current wheeze	Scoring variables	Exchange item 3 "wheeze without colds" with "wheezing or whistling in the chest in the last 12 mo"
L4	Altered outcome		
L4.1	Severity: Wheeze past 12 mo more than 4 episodes and use of asthma medication	Outcome	More than 4 episodes of wheeze past 12 mo and use of asthma medication past 12 mo

ALSPAC, Avon Longitudinal Study of Parents and Children; *LRC*, Leicestershire Respiratory Cohort.

TABLE E2. Comparison of 4 asthma prediction tools for preschool children

	PARC	API*	Isle of Wight	PIAMA
No. (included in analysis)	1226	776	336	2054
Inclusion criteria				
Age (y)	1-3	2-3	4	1-4
Symptoms	Health care visit because of respiratory problems plus ≥1 of the following: wheeze, cough without colds, cough at night	Entire cohort (including a majority of children without symptoms)	Wheeze at ages 1, 2, and 4 y	Wheeze or cough at night without colds in the past 12 mo
Outcome definition				
Age (y)	6-8	8	10	7-8
Prediction interval (y)	5	5	6	3-7
Criteria	Wheeze plus asthma medication (past 12 mo)	Doctor's diagnosis of asthma plus current wheeze or >3 episodes of wheeze (past 3 mo)	Current wheeze	At ages 7 and 8 y: current wheeze or prescription of inhaled corticosteroids or doctor's diagnosis of asthma (past 12 mo)
Outcome prevalence	28%	14%	37%	12%
Predictor variables included in tool	Male sex, age, wheeze without colds, frequent wheeze, activity disturbance, shortness of breath, exercise-related wheeze/cough, aeroallergen-related wheeze/cough, eczema, parental asthma, or bronchitis	Wheeze, frequent wheeze, wheeze without colds, eczema, parental asthma, blood eosinophilia, allergic rhinitis	Family history of asthma, recurrent chest infections (at 2 y), skin prick test positive (at 4 y), nasal symptoms (at 1 y)	Male sex, post term delivery, wheeze/dyspnea without colds, frequent wheeze, eczema, respiratory infections, inhalation medication (parents), parental education
Method used to derive tool	Penalized logistic regression	Combination of predictors was chosen that yielded the highest PPV and specificity	Stepwise backward logistic regression	Stepwise backward logistic regression
Performance measures	Score cutoff ≥5	Loose API	Score cutoff ≥3	Score cutoff ≥20
Youden index	0.43	0.32	0.38	0.36
Sensitivity (%)	72	51	53	60
Specificity (%)	71	81	85	76
PPV (%)	49	29	68	23
NPV (%)	86	91	74	94
LR+	2.48	7.43	3.41	2.50
LR−	0.39	0.75	0.56	0.53

API, Asthma Predictive Index; *LR+*, positive likelihood ratio; *LR−*, negative likelihood ratio; *NPV*, negative predictive value; *PARC*, Predicting Asthma Risk in Children; *PIAMA*, Prevalence and Incidence of Asthma and Mite Allergy; *PPV*, positive predictive value.

PARC,[E3] API,[E4] Isle of Wight risk score,[E5] PIAMA risk score,[E6] and Youden index reported for cutoff where the sum of sensitivity and specificity was maximal. It is possible that a higher sum of sensitivity and specificity exists at a cutoff point that was not reported in the respective studies.

*To have a prediction interval comparable with the one in our tool, we focused here on the API for prediction at 8 y.

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8 Discussion

8.1 Summary of main findings

Publication 1: The Swiss Paediatric Airway Cohort (SPAC)

The SPAC study is an observational clinical cohort of children with respiratory symptoms, and it is the first of its kind in Switzerland. The SPAC study includes children referred to paediatric respiratory outpatient clinics for respiratory symptoms such as wheeze, cough, dyspnoea, sleep- or exercise-related breathing problems. Excluded are children with a prior diagnosis of severe lung disease, such as cystic fibrosis, primary ciliary dyskinesia, or severe heart or oncological disease. The SPAC study comprises a wide range of data sources including parental questionnaires filled at baseline and each year following inclusion; referral letters sent by the referring physician; and final letters written by the outpatient clinic physicians including information about diagnoses, symptom history, results from diagnostic investigations, and suggested management. The SPAC study currently includes close to 2000 patients from eight hospitals and two private pulmonology practices.

Publication 2: Diagnosis in children with exercise-induced respiratory symptoms: a multi-centre study

In this cross-sectional multi-centre study of children referred for EIS, I found that almost half of the children got another diagnosis at the outpatient clinic than their suspected referral diagnosis. Among the 214 included children, 115 (54%) were diagnosed with asthma, 35 (16%) were diagnosed with extrathoracic dysfunctional breathing, 22 (10%) were diagnosed with thoracic dysfunctional breathing, 23 (11%) were diagnosed with asthma plus dysfunctional breathing, 10 (5%) were diagnosed with insufficient fitness level, 6 (3%) were diagnosed with chronic cough, and 3 (1%) got other diagnoses. Children diagnosed with dysfunctional breathing (with or without asthma) were slightly older, more often female, and had a lower BMI z-score than children diagnosed exclusively with asthma. The diagnostic tests most often performed were spirometry (97%), body plethysmography (80%), and measurements of exhaled nitric oxide (93%). Exercise-challenge test was performed in 80 (37%) of the children. Inhaled asthma medication (SABA, ICS, LABA) was prescribed to 93%

of children who were diagnosed with asthma. Physiotherapy was recommended in around half of the children diagnosed with dysfunctional breathing. Follow-up visits at the outpatient clinic were planned in 80% of children diagnosed with asthma and in 23% with extrathoracic dysfunctional breathing, 9% of those with thoracic dysfunctional breathing, 57% in those with dysfunctional breathing plus asthma, and in 16% of those with other diagnoses. The relative frequency of final diagnosis and diagnostic tests performed differed between clinics.

Publication 3: Reported symptoms differentiate diagnoses in children with exercise-induced respiratory problems: findings from the Swiss Paediatric Airway Cohort (SPAC)

In this study I found that parent reported symptoms helped distinguish diagnoses in children with EIS. Of the type of symptoms reported by parents, cough and dyspnoea best distinguished diagnoses. Cough was reported less for children with thoracic dysfunctional breathing (Relative Risk Ratio (RRR) 0.3, 95%CI 0.1-0.7) and asthma plus dysfunctional breathing (RRR 0.3, 95%CI 0.2-0.6) than for children with isolated asthma. Dyspnoea was reported more often for children with thoracic dysfunctional breathing (RRR 5.3, 95%CI 1.2-22) and asthma plus dysfunctional breathing (RRR 4.4, 95%CI 1.3-15), but less often for children with cough and other diagnosis (RRR 0.6, 95%CI 0.3-0.9) than for children with isolated asthma. Compared to children with asthma, swimming was more commonly reported as trigger for children with thoracic dysfunctional breathing (RRR 2.8, 95%CI 1.3-6.1), asthma plus dysfunctional breathing (RRR 2.1, 95%CI 1.1-4.1), and other diagnosis (RRR 2.0, 95%CI 1.2-3.4) than for children with isolated asthma. Also, characteristics of EIS differed between diagnoses. Late onset of EIS (after exercise) was rarely reported for extrathoracic DB (RRR 0.1, 95% CI 0.02-0.5), than for children with isolated asthma. A long duration of EIS (more than 10 minutes) was reported mostly for children with thoracic dysfunctional breathing (RRR 4.7, 95% CI 1.3-16.2) than for children with asthma. For localisation of dyspnoea (chest or throat), we saw little difference between diagnosis groups apart from children with extrathoracic dysfunctional breathing in which localisation was reported to be throat (RRR 2.4, 95% CI 1.0-6.0) more often than chest. Respiration phase (inspiration or expiration) did not differ between diagnosis groups. Use of a bronchodilator made symptoms disappear in close to half of the children with asthma (43%) and much less

in children with extrathoracic dysfunctional breathing (15%), thoracic dysfunctional breathing (22%), and chronic cough (17%).

Publication 4: EIS reported by physicians in the clinical history

In this study I found that physicians reported information on any EIS in 189 (96%) of 196 children referred primarily for EIS to paediatric respiratory outpatient clinics. Type of physical activities that trigger EIS was reported in 69%, the localisation of symptoms (chest or throat) in 48%, the respiration phase (inspiration or expiration) in 45%, the onset of EIS (during or after exercise) in 37%, whether a bronchodilator was used for EIS in 94% and their effect in 88%. Overall, triggers of EIS and characteristics of EIS were reported more often for children finally diagnosed with dysfunctional breathing than children diagnosed with isolated asthma. Comparisons between physician reported EIS with parent reported EIS showed that parents reported symptoms more often than physicians. For example, exercise-induced cough was reported by physicians in the clinical history for 35%, but by parents for 57%. The agreement between physician and parental reported EIS was moderate for use of bronchodilators (kappa(k)=0.53) and poor to fair for all other symptoms. For type of symptoms, the agreement was best for wheeze (k=0.24) and cough (k=0.39). For type of exercise triggers, agreement was best for swimming (k=0.22) and worst for intensive sport games (k=0.01). Localisation had better agreement (k=0.36) than respiration phase (k=0.13). Agreement between physician and parent reported EIS differed depending on who filled in the questionnaire for single items but agreement was not systematically better for either of the categories (questionnaire filled in by mother, father or other, or child helped).

Publication 5: The Simple 10-Item Predicting Asthma Risk in Children Tool to Predict Childhood Asthma – An External Validation

The simple 10-item Predicting Asthma Risk in Children (PARC) tool predicted asthma at school age equally well in the validation cohort ALSPAC (AUC 0.77) compared with the development cohort LRC (AUC 0.78). In ALSPAC, the score cutoff maximizing the sum of sensitivity (69%) and specificity (76%) was 4, and in LRC, the best cutoff was 5 (sensitivity 72% and specificity 71%). The overall model performance was similar in ALSPAC and LRC. The

max-scaled Brier score was 0.13 in ALSPAC and 0.22 in LRC, and Nagelkerke's R^2 was 0.23 in ALSPAC and 0.28 in LRC. The calibration assessment showed that PARC scores from the ALSPAC population were associated with a lower frequency of later asthma than predicted from the LRC. After recalibrating the predicted probabilities of the PARC model in ALSPAC, we found a Brier score of 0.17. Our sensitivity analyses showed good robustness of PARC in predicting school age asthma in ALSPAC as changes in inclusion criteria, prediction score items, and definitions of outcome only resulted in minor changes for most performance measures.

8.2 Strengths and limitations

Strengths and limitations related to the single projects are described in the publications listed in chapter 7. Here I describe strengths and limitations that relate more broadly to this PhD project.

Swiss Paediatric Airway Cohort

The main overall strength of this PhD project was the use of data from the SPAC study, which I helped set up during my PhD. However, although SPAC is a novel study including a large sample size, certain aspects of the study represented limitations in this PhD project. Below, I discuss strengths and limitations of the SPAC study that are related to the study design, recruitment, study management, and data sources.

Study design

The broad inclusion criteria of the SPAC study were a strength of this PhD as they made it possible to study children referred for any kind of EIS, and not only children suspected to have asthma or ILO. To our knowledge, all published studies describing diagnosis given to children referred for EIS include selected samples of children (71, 77, 85, 86, 106, 107). For example, several studies included children referred for EIS in which a trial with SABA had no effect, while others included children specifically suspected to have ILO. The observational design of SPAC in which no procedures were performed specifically for the study was a

strength of this PhD as it allowed me to study health care provision in children seen for EIS. Another strength of the observational design was that participation in the SPAC study required no extra procedures done at the hospital, and the parents only had to fill in a questionnaire. This might have resulted in our relatively high response rate of 61% as parents did not need to invest much time in the study and their children did not have to go through unnecessary testing. The SPAC study recruited 1893 patients from July 2017 to January 2020, which is more than for example the All Age Asthma cohort (ALLIANCE) did in the same amount of time. The ALLIANCE recruited 415 paediatric patients between September 2013 and December 2016 (108). In the ALLIANCE study, contrary to SPAC, patients performed a standard set of objective tests including lung function tests and biological samples, and additional data was collected through parental questionnaires and interviews. These more extensive participation requirements might have made it more difficult to recruit patients.

A limitation of the observational design was that it restricted the possibilities for certain analyses. Diagnostic investigations in children included in SPAC were performed by indication, which meant that not all children performed the same diagnostic tests. It was therefore not possible in children referred for EIS to compare results of the different diagnostic tests performed at the outpatient clinic by final diagnosis and analyse diagnostic accuracy. This would have resulted in bias by indication, in which diagnostic accuracy differs in patients who have the diagnostic test performed compared to patients who do not have the diagnostic test performed (109).

Recruitment procedures

A limitation of the observational design of SPAC was that recruitment procedures were adapted to each hospital to fit different systems for inviting and managing patient visits. Some patients received study documents at home before the clinical visit while others received study documents during the visit to the outpatient clinic. Both recruitment systems worked well, but we saw higher response rates in the clinics where patients received the documents before their clinical appointment (e.g. Lucerne and St. Gallen) compared with response rates in the clinics where patients received the documents during the clinical appointment (e.g. Zurich). This might have affected the representation of the study

population as patients that received documents before their clinical appointment had time to go through the SPAC study documents and the physicians therefore had more time to answer specific questions during the visit. In the clinics, where patients were invited directly at the clinical appointment, physicians would need more time to explain the overall purpose of the study and would have less time to answer specific questions. Also, parents receiving documents prior to the appointment were asked to fill in the baseline questionnaire and give it to the physician during the clinical visit, while parents who got the SPAC study documents at the clinical appointment were asked to send the completed questionnaire by post after the appointment. This might have led to less people filling in the SPAC study documents and sending them by post, although we sent reminders. **Table 3** (chapter 6) displays differences in population characteristics between clinics. Children recruited in the clinics where the SPAC study documents were sent before the clinical appointment were younger and parents less often had a university degree. However, the difference in response rates and population characteristics between clinics may also reflect the different population composition in different areas in Switzerland. For example, the number of people with a university degree are higher in cities with more universities. The differences in recruitments procedures did however not seem to affect the proportion of parents reporting EIS in the questionnaire (table 3), and the results from this PhD thesis that focuses mainly on exercise-induced problems may therefore not have been strongly affected by possibly recruitment differences between clinics.

Recruitment areas

SPAC included patients from all major paediatric hospitals in the German-speaking part of Switzerland, which enabled us to compare diagnostic practices and management between clinics. Our results can be generalized to children living in the German speaking part of Switzerland. By the time, data was extracted for this PhD, no SPAC data was collected from the French or Italian speaking parts of Switzerland. However, the University Children's hospital in Lausanne started the recruitment of patients into SPAC in November 2019, and the arrangements for starting recruitment in the University Children's hospital in Geneva will start in February 2020. The SPAC study aims to represent children referred to paediatric respiratory outpatient clinics in the whole of Switzerland.

Data sources

The SPAC study comprises a vast array of data sources, which was a strength of this PhD. For studying children with EIS, I used information about suspected referral diagnosis from the referral letter sent to the outpatient clinic. I used information from the outpatient clinic including diagnosis, symptom history, diagnostic tests performed, and prescribed treatment. Finally, I used data from the parental questionnaire administered to all patients in SPAC. I could therefore describe children referred for EIS including both information reported by the physicians and by the parents. To my knowledge, no studies in children referred for EIS included such vast amounts and detailed information.

All data sources have their limitations. A limitation of the questionnaire data was, that the questions asking about EIS had not been validated among parents in Switzerland. At the time, when we developed the parental questionnaire, no validated questions on EIS existed in German apart from the ISAAC question asking about wheeze during exercise (110). We therefore included questions that are usually asked in a clinical consultation, of which many are also recommended for evaluating children with exercise-induced problems (13, 97). The questionnaire, however, was sent to collaborating clinicians, and to other collaborators with children to test the questionnaire before use.

For publication 2, 3, and 4, I used data on final diagnosis given at the outpatient clinics. Data on final diagnosis was taken from the letter written by the outpatient clinic pulmonologist that is sent to the referring physician after the appointment at the outpatient clinic. This was a limitation, as the final diagnosis was not based on a standardized predefined diagnostic algorithm, however all pulmonologists were board-certified and diagnoses were based on clinical history and standardized diagnostic test results.

8.3 Interpretation of main findings

The SPAC study is a unique observational clinical cohort study embedded in routine care investigating a broad spectrum of children referred to paediatric respiratory outpatient clinics with respiratory symptoms. The SPAC study combines routinely collected data from the outpatient clinics with patient reported information from standardized questionnaires at

baseline and through yearly follow-ups. It forms the basis for epidemiological and clinical research in the fields of pathophysiology, clinical phenotypes, and long-term course of common respiratory problems in children. Additionally, the SPAC study will serve as a platform for future nested studies.

In half of the children referred for EIS, the final diagnosis given at the outpatient clinic differed from the suspected referral diagnosis. This highlights the importance of referring children with EIS for further diagnostic evaluation. The commonest diagnosis given at the outpatient clinic apart from asthma, was extrathoracic and thoracic dysfunctional breathing, which was diagnosed in about 40% of the children. However, dysfunctional breathing was only suspected at referral in 6% of the cases. It is important that dysfunctional breathing receives more attention among primary care physicians for early diagnosis and symptom control. The majority of children referred for EIS performed basic investigations for asthma like FeNO, allergy tests, and lung function testing (spirometry and body plethysmography). Exercise challenge testing was performed in one third of the children. Further tests (such as cardiopulmonary exercise test or flexible laryngoscopy) that might be considered diagnostic for other aetiologies than asthma were not observed. Management proposed at the outpatient clinic was inconsistent between clinics and diagnosis groups. Most children diagnosed with asthma were prescribed a bronchodilator, which is recommended in children with asthma. The recommended management of dysfunctional breathing is physiotherapy, but only around half of children diagnosed with dysfunctional breathing were referred to physiotherapy. This may be because physicians considered the disease as mild and selected a wait-and-see policy after carefully informing the patients about the benign aetiology of the symptoms. Follow-up visits at the outpatient clinics were planned for most children with asthma, but only for 23% of children diagnosed with extrathoracic dysfunctional breathing and 9% with thoracic dysfunctional breathing. Summing up, this highlights the need for diagnostic and management guidelines in children seen for EIS. Comparable guidelines already exist for primary ciliary dyskinesia (111) and a European Respiratory Society task force is currently developing a guideline for childhood asthma.

Parent reported EIS were helpful to distinguish diagnoses in children with EIS. In particular, the type of EIS (especially cough and dyspnoea), triggers of EIS (especially swimming), and characteristics (onset of symptoms, localisation of dyspnoea, and use of inhaled medication) were helpful. In contrary, respiration phase (inspiration or expiration) and duration of symptoms were not helpful. This study was the first to compare reported symptoms between more than two diagnosis groups, and the first study to investigate whether physical activities that trigger EIS are helpful to distinguish diagnoses of EIS. Type of EIS (especially cough and dyspnoea) were better at distinguishing thoracic dysfunctional breathing from asthma than extrathoracic dysfunctional breathing from asthma. This highlights why extrathoracic dysfunctional breathing might be misdiagnosed as asthma (77, 85). Although this study used one of the largest samples to compare reported symptom between diagnoses in children with EIS, I did not have statistical power to study whether combinations of symptoms are better at distinguishing diagnoses than single symptoms. Future studies should also assess the accuracy of objective diagnostic tests in combination with reported symptoms to diagnose children with EIS.

Physicians reported EIS in the clinical history in almost all children but information on triggers (e.g. running, swimming) were reported in only two thirds of the children, and characteristics (localisation, respiratory phase, onset of EIS, and use of inhaled medication) were reported in half of the children. Triggers and characteristics of EIS were reported more often in children who were diagnosed with extrathoracic and thoracic dysfunctional breathing than children diagnosed with asthma. Several studies have described how knowledge on characteristics can help diagnose EIS (13, 15, 97), which highlights why especially this information should be reported by physicians in the clinical history. I found poor to moderate agreement between physician and parent reported EIS, which may be partly due to differences in how EIS were reported by physicians (free text in clinical history) and by parents (prompted for each question in a standardized questionnaire). This might also explain why parents reported symptoms and triggers of EIS more often than physicians. Overall, this study showed that there is potential for improvement regarding reporting of EIS by physicians in medical records, which in turn could be helpful for diagnosing children with

EIS. A semi-structured interview guide could help to improve the completeness of EIS reported in the clinical history.

The PARC tool to predict childhood asthma predicted asthma equally well in the validation cohort compared with the development cohort. The predicted probabilities of the tool had to be recalibrated to predict asthma correctly in the validation cohort, because the outcome prevalence was lower than in the development cohort. The PARC tool was previously externally validated in the Multicentre Allergy Study (MAS-90), where it showed better predictive properties (AUC=0.83) than in LRC or ALSPAC. The MAS-90 study population was smaller (n=140) and comprised a high-risk cohort of children with maternal history of asthma. Results from the external validation studies in MAS-90 and the ALSPAC show that PARC is robust in predicting asthma in different study populations. Exercise as trigger for wheeze was included in the original PARC tool, and remained important after external validation. This emphasizes the importance of reporting exercise-induced symptoms in children independent from aetiology and final diagnosis.

8.4 Outlook

The results of this PhD project have added to the knowledge of EIS in childhood, however open questions remain. While several studies have focused on persistence of symptoms in children with wheeze (112, 113), no studies to my knowledge report on prognosis in children seen for EIS of different aetiologies. Exercise-induced wheeze is a good predictor for wheeze later on in children suspected to have asthma (114, 115), however whether other type of symptoms (dyspnoea or cough) have the same prognostic properties is unknown. Symptom persistence and prognosis is also not well described in children with extrathoracic and thoracic dysfunctional breathing. Intervention studies show that breathing retraining improve quality of life in adults with severe ILO, however no studies of that kind exist in children. A study on prognosis in children with EIS could be conducted using data from SPAC by analysing data on reported symptoms from the yearly follow-up questionnaires.

In this PhD project, I found that the diagnostic tests performed in children referred for EIS differed considerably between clinics. This indicates a lack of consensus on the best

approach to diagnose children with EIS; a lack of consensus that reflects a lack of published evidence on the topic. Several studies discuss the best approach to diagnose exercise-induced bronchoconstriction (116), or functional dysfunctional breathing disorders (97), however no studies have investigated the best approach to diagnose children presenting with EIS. A study like this could be nested within the SPAC study, in which all children referred specifically for exercise-induced respiratory problems would receive a standardized set of diagnostic tests and thereafter get a diagnosis. Diagnostic accuracy could then be assessed and a proposal for an algorithm to diagnose children with EIS could be proposed.

In my PhD project, I found that detailed information about EIS could help differentiate diagnoses in children with EIS. Detailed information about EIS, however, are not only relevant for diagnosis, they would also be relevant for research areas such as intervention research. For example, a study examining the effect of physiotherapeutic interventions for EIS would need validated questions to measure change in symptoms over time. I showed that the questions asking about EIS that were included in the SPAC questionnaire differentiated diagnoses as expected for many of the questionnaire items. However, we found unexpected distributions of answers in the questionnaire items asking about respiration phase (inspiration and expiration), localisation of symptoms (chest and throat), and duration of symptoms. This could indicate that either the questions asked were not clear enough for the parents, or the parents didn't know the correct answer to these questions. We did not include cold-weather sports as a question asking about triggers for EIS, a trigger that was reported by physicians in the clinical history. Also, type of symptoms such as dizziness and headache were not included in the questionnaire, symptoms that were described by parents in a free text field. I would recommend to conduct a study that further develops questions to measure EIS in children living in Switzerland where both reliability and validity are tested including content, construct, and external validity.

8.5 Conclusions

In summary, this PhD project led to the development of a large cohort study (SPAC) in which I studied children with EIS. My main findings were that many children referred for EIS were diagnosed with dysfunctional breathing, which is rarely suspected at time of referral. It is important that dysfunctional breathing receives more attention among primary care

physicians for early diagnosis and symptom control. Diagnosis, diagnostic investigations, and management in children with EIS differed between outpatient clinics and diagnostic groups. Along with inconsistent reporting of EIS by physicians in the medical records, the results from this PhD thesis indicate a need for guidelines on the diagnosis and management in children with EIS. Apart from studying clinical practice, I also studied EIS reported by parents and found that reported symptoms can be useful for distinguishing diagnoses in children with EIS. Overall, this PhD helped to fill knowledge gaps in the field of EIS in children, however open questions remain. Future research should focus on the development of an algorithm to diagnose children with EIS and investigate prognosis and impact of EIS on health related factors such as quality of life and physical activity.

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10 Related publications

10.1 Co-author publication: Temporal stability of multitrigger and episodic viral wheeze in early childhood

Spycher BD, Cochrane C, Granell C, Sterne JAC, Silverman M, **Pedersen E**, Gaillard EA, Henderson AJ, Kuehni CE.

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Temporal stability of multitrigger and episodic viral wheeze in early childhood

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@ERSpublications
Multitrigger and episodic viral wheeze tend to persist in early childhood and may reflect distinct disease processes http://ow.ly/KQrk30fvXMj

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ABSTRACT The distinction between episodic viral wheeze (EVW) and multitrigger wheeze (MTW) is used to guide management of preschool wheeze. It has been questioned whether these phenotypes are stable over time. We examined the temporal stability of MTW and EVW in two large population-based cohorts.

We classified children from the Avon Longitudinal Study of Parents and Children (n=10 970) and the Leicester Respiratory Cohorts ((LRCs), n=3263) into EVW, MTW and no wheeze at ages 2, 4 and 6 years based on parent-reported symptoms. Using multinomial regression, we estimated relative risk ratios for EVW and MTW at follow-up (no wheeze as reference category) with and without adjusting for wheeze severity.

Although large proportions of children with EVW and MTW became asymptomatic, those that continued to wheeze showed a tendency to remain in the same phenotype: among children with MTW at 4 years in the LRCs, the adjusted relative risk ratio was 15.6 (95% CI 8.3–29.2) for MTW (stable phenotype) compared to 7.0 (95% CI 2.6–18.9) for EVW (phenotype switching) at 6 years. The tendency to persist was weaker for EVW and from 2–4 years. Results were similar across cohorts.

This suggests that MTW, and to a lesser extent EVW, tend to persist regardless of wheeze severity.

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Introduction

There is debate whether recurrent wheezing in young children represents a single disease entity, 'childhood asthma', or a heterogeneous group of disorders, referred to as asthma 'phenotypes'. Numerous attempts have been made to distinguish phenotypes [1–3]. A commonly used classification is the distinction between episodic viral wheeze and multitrigger wheeze [4, 5]. Episodic viral wheeze (EVW), also called exclusive viral wheeze, characterises children who wheeze only during respiratory infections. During the intervals between colds, these children are asymptomatic. EVW is frequent in infancy and preschool years, and less prevalent in older children [6], and has also been described in adults [7]. Multitrigger wheeze (MTW) more closely resembles classical asthma [8]. Children with MTW also wheeze between respiratory infections in response to a variety of factors, including allergens, exercise, laughing or crying, strong smells or certain foods or drinks [9]. MTW is more strongly associated with lung function abnormalities [8] and atopy [10]. While most children with EVW become asymptomatic, MTW tends to persist [11, 12]. This two-phenotype model has been used to inform the management of preschool wheeze [9, 13–16]. For instance, a European Respiratory Society (ERS) taskforce recommended using inhaled corticosteroids for maintenance treatment of MTW, but montelukast for EVW [9].

The distinction between EVW and MTW and its usefulness for the management of preschool wheeze has been challenged [17, 18]. Garcia-Marcos and Martinez [19] suggested that the two phenotypes merely reflect the ends of a severity spectrum, with MTW representing more severe wheeze. Severity of wheeze, in particular frequency of episodes, strongly predicts long-term prognosis [12, 20, 21]. It has also been questioned whether these phenotypes are sufficiently stable over time to represent clinically meaningful entities [22, 23]. In an update of their 2014 recommendations, the ERS taskforce pointed out that wheeze patterns in young children vary over time and with treatment, rendering the distinction between EVW and MTW difficult in many patients [17]. Consequently, inhaled corticosteroids remained the first-line treatment for MTW, but were also recommended for patients with frequent or severe EVW. The taskforce concluded that future research should focus on disease severity in addition to phenotypes [17].

The current study used longitudinal data on wheezing at ages 2, 4 and 6 years from two large population-based birth cohorts, to examine the stability of MTW and EVW over time, and the degree to which stability was explained by differences in wheeze severity.

Materials and methods

Study populations

ALSPAC (Avon Longitudinal Study of Parents and Children) is a longitudinal population-based birth cohort study that recruited 14 541 pregnant women resident in Avon, UK, with expected dates of delivery between April 1991 and December 1992. There were 14 062 live-born children. The study has been described in detail elsewhere [24]. Each year up until the children were 8 years of age, the study mothers were sent child health questionnaires including detailed questions on respiratory symptoms. Ethical approval was obtained from the ALSPAC Ethics and Law Committee and from local research ethics committees.

The Leicester 1998-b respiratory cohort (LRC) consists of a population-based random sample of 4300 children born between May 1996 and April 1997 in Leicestershire, UK. It is described in detail elsewhere [25]. Perinatal routine data were obtained from the Leicestershire Health Authority Child Health Database, and mothers were sent questionnaires including detailed questions on respiratory symptoms in 1998, 1999, 2001, 2003, 2006 and 2010. The study was approved by the Leicestershire Health Authority Research Ethics Committee.

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We included all children in both cohorts whose parents responded to a questionnaire sent at age 2, 4 or 6 years (or a questionnaire sent at age 30, 57 and 81 months for ALSPAC).

Definition of wheeze phenotypes

The questions used to address wheeze or whistling in the previous 12 months ('current wheeze') were similar in both cohorts (table 1). Children were assigned to the EVW phenotype if they reported current wheeze in the previous 12 months with infections as a trigger and no other triggers (table 1). Children with current wheeze in the previous 12 months reporting a trigger category other than infections were assigned to MTW. Children with current wheeze who could not be assigned either to EVW or MTW were designated non-classifiable.

Information on wheeze severity

We defined the following indicators of wheeze severity based on symptoms in the previous 12 months: frequent wheeze attacks (⩾3 in ALSPAC, ⩾4 in LRC), shortness of breath during wheeze attacks, sleep disturbed due to wheezing, speech limited to one to two words at a time between breaths due to wheeze (ALSPAC only), and wheeze interfering with the child's daily activities (LRC only). The questions used to assess this information and the definitions of severity indicators are provided in supplementary table S1.

Statistical analysis

We carried out the following analysis steps:

1) We computed the prevalence of current wheeze, EVW and MTW at ages 2, 4 and 6 years.

2) At each age, we assessed the association between wheeze phenotypes and dichotomous indicators of severity (supplementary table S1) by calculating the odds ratios for MTW *versus* EVW, comparing severe with less severe wheeze using logistic regression.

3) For each age interval (2–4, 4–6 and 2–6 years), we assessed whether wheeze phenotype at the first time point (baseline) predicted current wheeze at the later time point (follow-up). We used logistic regression

TABLE 1 Questionnaire items and definitions of wheeze phenotypes in the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Leicester Respiratory Cohort Study (LRC)

	ALSPAC	LRC
Current wheeze	1) "Since your child was [age at previous questionnaire] old, has he/she had any periods when there was wheezing with whistling on his chest when he breathed?" (yes/no) 2) Has he/she had "wheezing" in the last 12 months? (yes/no) Definition of current wheeze: positive response to 1) or 2)	1) "Has your child had wheezing or whistling in the chest in the last 12 months?" (yes/no) Definition of current wheeze: positive response to 1)
Triggers of wheeze	3) "What do you think brings on the wheezing attacks?" a) chest infection or bronchitis b) being in a smoky room c) cold weather d) I don't know e) other (please describe) Responses to 2e) were coded into the following categories: f) infections (upper or lower RTI) g) allergic triggers (airborne allergens, foods and beverages) h) physical activities or intense emotions i) damp or cold indoors or weather conditions j) air pollution k) asthma (diagnosed, suspected, family history) l) other (*e.g.* hot temperature, irritants, teething)	2) "In the last 12 months, has your child had wheezing or whistling in the chest during or soon after a cold or flu?" (yes/no) 3) "In the last 12 months, has your child had wheezing or whistling in the chest even without having a cold or flu?" (yes/no) 4) "In the last 12 months, did the following things cause wheezing in your child?" a) exercise (playing or running) b) laughing, crying or excitement c) contact with pets or other animals d) pollen (grass, hay, trees, flowers)[#] e) food or drinks (answer categories for a–d: yes/no/don't know)
Phenotype definitions[¶]	EVW: 1 or 2 and 3a or 3f with no other categories reported MTW: 1 or 2 and any of 3b, 3c, 3g–3j or 3l NCW: 1 or 2 and no response to 3, or 3d or 3k with no other categories reported	EVW: 1 and 2 with no positive response to any of 3, 4a–4e MTW: 1 and any of 3, 4a–4e NCW: 1 and no positive response to any of 2, 3, 4a–4e

RTI: respiratory tract infection; EVW: episodic viral wheeze; MTW: multitrigger wheeze; NCW: non-classifiable wheeze.[#]: only asked from age 4 years onwards; [¶]: positive responses to listed questionnaire items required.

to estimate the odds ratios for current wheeze at follow-up, comparing children with EVW and MTW at baseline with those without wheeze.

4) For each age interval, we assessed whether children tended to have the same wheeze phenotypes at follow-up as they did at baseline. We first calculated the probability for these categories at follow-up given the category at baseline. Using multinomial logistic regression, we then estimated the relative risk ratios (RRRs) for EVW and MTW at follow-up, comparing these phenotypes with no wheeze at baseline. We adjusted the regression models for symptom severity (original variables, not dichotomised) at baseline to determine whether the phenotypes at baseline predicted the phenotypes at follow-up independent of severity. In separate models we additionally adjusted for sex, ethnicity (white, other), maternal smoking during pregnancy, older siblings (yes/no), crowding (>1 person/room) and pet ownership. The RRRs compared the risk ratio for phenotypes at follow-up (probability of having the phenotype divided by probability of having no wheeze) in children of a given phenotype at baseline (EVW or MTW) to children with no wheeze at baseline. We also tested for the equality of RRRs between EVW and MTW at baseline. Such equality implies absence of phenotype persistence. For instance, equality of RRRs for EVW at follow-up means that after excluding children with MTW at follow-up, those with EVW and MTW at baseline are equally likely to have EVW at follow-up.

Results

Of the 14 062 live-born children recruited in ALSPAC, we included 10 970 (78%) for whom information on wheeze was available for at least one time point (age 2, 4 or 6 years). Information on wheeze was provided for 9953, 9391 and 8393 children at the ages of 2, 4 and 6 years (table 2). Similarly, of the 4300 children in the LRC (1998-b cohort), we included 3263 (76%) and information on wheeze was reported for 2355, 2609 and 2077 at ages 2, 4 and 6 years respectively.

The cohorts differed with respect to ethnicity and socioeconomic conditions (table 2). In ALSPAC, 97% of the children were white. In the LRC, 85% were white and 15% of South Asian origin. Households in the LRC tended to be more crowded, and maternal smoking and pet ownership were less common than in ALSPAC. The proportions of children whose mothers smoked during pregnancy, who had older siblings

TABLE 2 Characteristics of the study populations (Avon Longitudinal Study of Parents and Children (ALSPAC) and the Leicester Respiratory Cohort (LRC) study) and prevalence of wheeze phenotypes at ages 2, 4 and 6 years

Characteristics	ALSPAC		LRC	
	n/N	%	n/N	%
Subjects	10 970		3263	
Sociodemographic data				
Male sex	5680/10 970	52	1692/3263	52
Ethnicity white[#]	10 266/10 574	97	2761/3263	85
Maternal smoking in pregnancy	2635/10 879	24	460/2865	16
⩾1 older siblings	5778/10 274	56	1837/2798	66
Crowding >1 person in room	2285/9406	24	1150/2852	40
Pet owner	5475/9805	56	1226/2903	42
Wheeze at 2 years of age				
Current wheeze	2261/9953	23	533/2355	23
EVW[¶]	752/1680	45	229/524	44
MTW[¶]	928/1680	55	295/524	56
Wheeze at 4 years of age				
Current wheeze	1780/9391	19	504/2609	19
EVW[¶]	519/1423	36	158/498	32
MTW[¶]	904/1423	64	340/498	68
Wheeze at 6 years of age				
Current wheeze	1129/8393	13	330/2077	16
EVW[¶]	236/779	30	79/325	24
MTW[¶]	543/779	70	246/325	76

EVW: episodic viral wheeze; MTW: multitrigger wheeze. [#]: in ALSPAC the remaining children are ethnically diverse while in LRC the remaining children are of South Asian origin. [¶]: denominator represents children with current wheeze that can be classified into EVW or MTW. Excludes children with non-classifiable wheeze (table 1) and thus does not equal the number with any current wheeze.

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or who lived in crowded homes were lower in children who participated in only one to two surveys than in those who participated in all three surveys, and lower still in children excluded from the analyses (supplementary table S2). Maternal smoking during pregnancy was more common among children with MTW than among those with EVW (supplementary table S3).

Prevalence of current wheeze and wheeze phenotypes at ages 2, 4 and 6 years

Prevalence of current wheeze in ALSPAC was 23% at age 2 years, and decreased to 13% at age 6 years (table 2). In the LRC, current wheeze decreased similarly from 23% at age 2 to 16% at age 6 years. The relative frequencies of the two phenotypes were remarkably similar in both cohorts. At age 2, 45% of all classifiable wheezers in ALSPAC (44% in the LRC) were defined as EVW; this decreased to 36% (32%) at age 4 and 30% (24%) at age 6.

Associations between wheeze phenotypes and indicators of wheeze severity

Severity of wheezing illness as defined by the five indicators (frequency of attacks, shortness of breath, sleep disturbance, interference with activities and speech limitation) was higher for MTW than for EVW (table 3). The difference between phenotypes was larger in the LRC than in ALSPAC. For example, at age 2, the odds ratio for having MTW rather than EVW, comparing children with frequent episodes of wheeze to those with less frequent episodes, was 2.7 (95% CI 2.2–3.2) in ALSPAC and 6.5 (95% CI 4.1–10.4) in the LRC. In the LRC, differences between the two phenotypes became more distinct (larger odds ratios) with age.

Risk of later wheeze in children with episodic viral wheeze and multitrigger wheeze

The risk of having current wheeze 2 or 4 years later was higher for MTW than for EVW in both cohorts (supplementary tables S4 and S6). In the ALSPAC cohort, the odds ratio for wheeze at age 4 was 7.8 (95% CI 6.5–9.3) for children with EVW at age 2 years, and 12.5 (95% CI 10.6–14.8) for those with MTW, compared to children who did not wheeze. In the LRC, the odds ratios were 3.7 (95% CI 2.6–5.3) and 9.9 (95% CI 7.2–13.5). Prediction of later wheeze was stronger from age 4–6 years: in ALSPAC, the odds ratios were 26.6 (95% CI 22.2–32.1) for MTW and 11.9 (95% CI 9.5–14.8) for EVW at baseline (supplementary table S4, crude odds ratios). When the regression models were adjusted for wheeze severity, the difference in prognosis between the two phenotypes diminished somewhat, particularly in ALSPAC (supplementary table S4, adjusted odds ratio). The odds ratios for current wheeze 4 years later (prediction from 2 to 6 years) were lower than for the 2-year prediction intervals (supplementary table S6).

TABLE 3 Association between wheeze phenotypes and symptom severity in the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Leicester Respiratory Cohort (LRC) at ages 2, 4 and 6 years

Indicators of symptom severity[#]	ALSPAC			LRC		
	EVW	MTW	MTW *versus* EVW[¶]	EVW	MTW	MTW *versus* EVW[¶]
Wheeze at 2 years of age n	752	928		229	295	
Frequent attacks	39.7	63.6	2.7 (2.2–3.2)	11.5	45.9	6.5 (4.1–10.4)
Shortness of breath	43.3	58.2	1.8 (1.5–2.2)	39.9	76.2	4.8 (3.3–7.0)
Sleep disturbance	NA	NA	NA	40.4	74.0	4.2 (2.9–6.1)
Interference with activities	NA	NA	NA	38.0	73.6	4.5 (3.1–6.6)
Wheeze at 4 years of age n	519	904		158	340	
Frequent attacks	45.3	74.0	3.4 (2.7–4.3)	7.6	40.0	8.1 (4.3–15.1)
Shortness of breath	50.2	64.1	1.8 (1.4–2.2)	NA	NA	NA
Sleep disturbance	NA	NA	NA	41.7	71.3	3.5 (2.3–5.2)
Interference with activities	NA	NA	NA	37.2	74.8	5.0 (3.3–7.5)
Wheeze at 6 years of age n	236	543		79	246	
Frequent attacks	39.6	64.7	2.8 (2.0–3.8)	5.1	41.1	12.9 (4.6–36.4)
Shortness of breath	53.0	61.3	1.4 (1.0–1.9)	NA	NA	NA
Sleep disturbance	52.4	62.4	1.5 (1.1–2.1)	43.0	67.4	2.7 (1.6–4.6)
Interference with activities	NA	NA	NA	29.1	78.7	9.0 (5.1–16.0)
Speech limitation	8.1	13.4	1.8 (1.0–3.0)	NA	NA	NA

Data are presented as % or OR (95% CI), unless otherwise stated. EVW: episodic viral wheeze; MTW: multitrigger wheeze; NA: not available. [#]: definitions of severity indicators are provided in supplementary table S1; [¶]: OR from logistic regression excluding children without wheeze or with non-classifiable wheeze.

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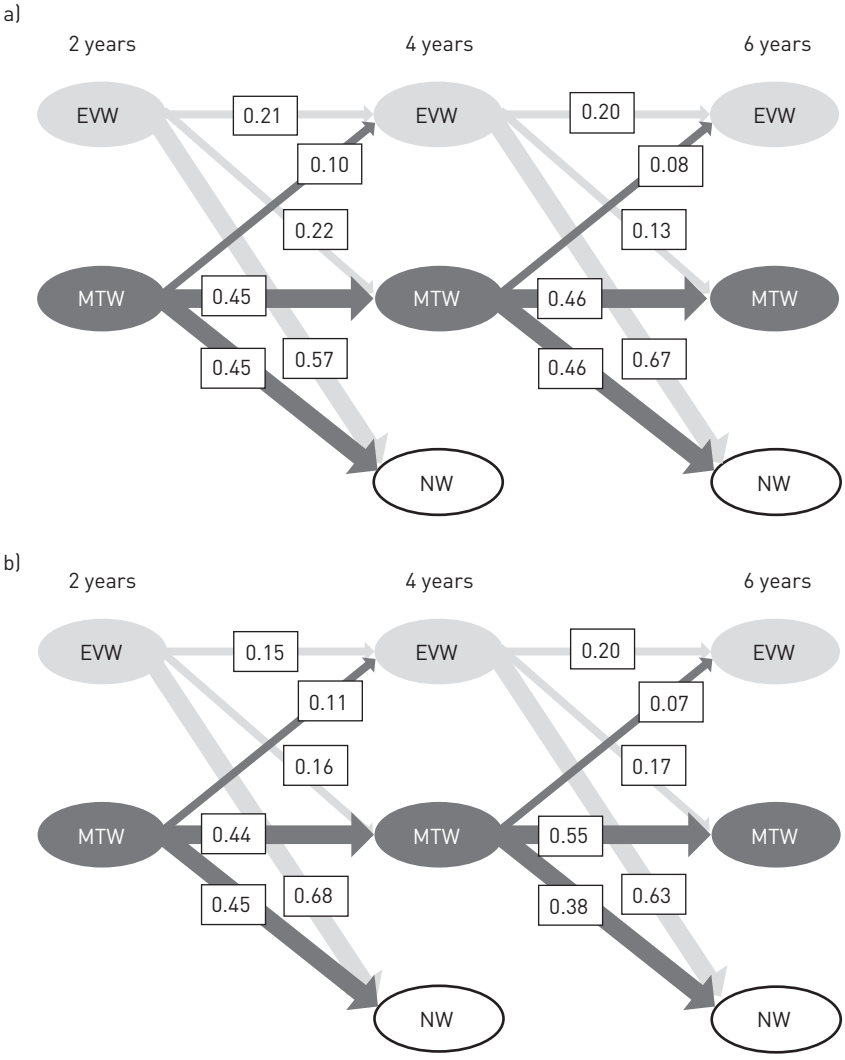

FIGURE 1 Transition probabilities from episodic viral wheeze (EVW) and multitrigger wheeze (MTW) to EVW, MTW and no wheeze (NW) for ages 2–4 years and ages 4–6 years in a) the Avon Longitudinal Study of Parents and Children and b) the Leicester Respiratory Cohort.

Likelihood of keeping or switching wheeze phenotype

The proportion of children remaining in their phenotype or transitioning to another phenotype was similar in the two cohorts (supplementary table S5 and figure 1). Among the ALSPAC children who had EVW at 2 years and who had a classifiable wheezing pattern 2 years later, 57% became asymptomatic, while 21% still had EVW and 22% had developed MTW. Among children with MTW at age 2, 45% became asymptomatic, 45% remained MTW and only 10% were reclassified to EVW.

Despite considerable proportions of children remitting or changing phenotype, multinomial logistic regressions showed a tendency of phenotypes to persist: RRRs were consistently higher for remaining in the same phenotype than for phenotype switching (table 4 and supplementary tables S5 and S7). Among children with EVW at age 2 years in ALSPAC, the crude RRR was 9.4 (95% CI 7.4–11.9) for EVW (stable phenotype) but 7.7 (95% CI 6.1–9.7) for MTW (phenotype switching) at 4 years. Among children with MTW at 2 years, the tendency for persistence was much stronger with a RRR for later MTW and EVW of 20.5 (95% CI 16.8–24.8) and 5.9 (95% CI 4.4–7.8), respectively. Phenotype persistence was stronger for both phenotypes from age 4 to age 6, and was strongest for MTW, with RRRs 44.9 (95% CI 35.4–56.9) and 27.3 (95% CI 18.9–39.6) in ALSPAC and the LRC, respectively. Although the RRRs diminished after adjustment for severity, they remained considerably higher for remaining in the same phenotype than for switching, particularly for MTW (table 4, adjusted RRR). Despite the larger proportions of children becoming asymptomatic, the RRRs for the 4-year period of age 2–6 years still revealed a tendency of phenotypes to persist (supplementary table S7). Additionally, adjusting regression models for

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TABLE 4 Likelihood of retaining the same phenotype or switching the wheeze phenotype with age in children in the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Leicester Respiratory Cohort (LRC)

	Age at baseline years	Age at follow-up years	Phenotype at baseline	EVW at follow-up				MTW at follow-up			
				Crude RRR[#] (95% CI)	p-value[¶]	Adjusted RRR[+] (95% CI)	p-value[¶]	Crude RRR[#] (95% CI)	p-value[¶]	Adjusted RRR[+] (95% CI)	p-value[¶]
ALSPAC											
	2	4	No wheeze	1	0.004	1	<0.001	1	<0.001	1	<0.001
			EVW	9.4 (7.4–11.9)		4.6 (3.3–6.4)		7.7 (6.1–9.7)		3.2 (2.3–4.3)	
			MTW	5.9 (4.4–7.8)		2.2 (1.5–3.3)		20.5 (16.8–24.8)		6.2 (4.6–8.4)	
	4	6	No wheeze	1	0.002	1	<0.001	1	<0.001	1	<0.001
			EVW	23.1 (16.5–32.3)		8.0 (4.9–13.1)		8.7 (6.2–12.3)		2.0 (1.2–3.3)	
			MTW	14.1 (9.8–20.5)		3.3 (1.9–6.0)		44.9 (35.4–56.9)		6.7 (4.3–10.4)	
LRC											
	2	4	No wheeze	1	0.868	1	0.564	1	<0.001	1	0.004
			EVW	4.9 (3.0–8.0)		4.1 (2.2–7.5)		3.1 (2.0–4.9)		1.8 (1.0–3.2)	
			MTW	5.1 (3.0–8.7)		3.3 (1.4–7.7)		12.9 (9.1–18.2)		4.1 (2.1–7.9)	
	4	6	No wheeze	1	0.114	1	0.074	1	<0.001	1	<0.001
			EVW	15.4 (8.1–29.1)		15.5 (7.3–32.9)		5.1 (2.8–9.3)		4.0 (2.0–8.0)	
			MTW	8.3 (4.2–16.4)		7.0 (2.6–18.9)		27.3 (18.9–39.6)		15.6 (8.3–29.2)	

EVW: episodic viral wheeze; MTW: multitrigger wheeze. [#]: relative risk ratios (RRRs) from multinomial regression analysis. To provide an example for the interpretation of the RRRs, assume that among non-wheezers at baseline the risks for EVW and no wheeze at follow-up are 4% and 90%, respectively. The relative risk (RR) for EVW among non-wheezers is thus 0.044. If, in children with EVW at baseline the corresponding risks are 20% and 60%, respectively, *i.e.* RR=0.333, this would translate to an RRR for EVW at follow-up of 7.5 (0.333/0.044). The regression analysis also included children with non-classifiable wheeze as a separate category (see table 1), but results for this category are not reported.[¶]: for tests of equality of RRR between EVW and MTW at baseline. Such equality implies absence of phenotype persistence. For instance, equality of RRR for EVW at follow-up means that after excluding children with MTW at follow-up, those with EVW and MTW at baseline are equally likely to have EVW at follow-up.[+]: adjusted for symptom severity at baseline (frequent attacks, shortness of breath, sleep disturbance, interference with activities and speech limitation).

sociodemographic variables and early environmental exposures only led to marginal changes in estimated RRRs (results not shown).

Statistical tests also support phenotype persistence. The p-values for equality of RRRs between EVW and MTW at baseline were all <0.01 except in the LRC for EVW at follow-up (table 4). These p-values remained low after adjusting for symptom severity.

Discussion

Using prospectively collected data from two independent population-based cohorts, our study found that children with MTW and EVW whose wheeze persisted over 2-year periods (ages 2–4 and 4–6 years) showed a tendency to remain in the same phenotype. This persistence was stronger for MTW than for EVW and was only partially explained by reported symptom severity. This supports the hypothesis that EVW and MTW represent distinct disease entities rather than different ends of a severity spectrum. Our study also confirms that a high proportion of early wheeze remits (approximately 60–70% of EVW and 40–45% of MTW). Despite differences in study design and methodology, results from the two cohorts were very similar.

Strengths and weaknesses of the study

Our study was based on two large, population-based cohort studies that assessed wheezing prospectively. This provided large representative samples and enabled us to use phenotype definitions that are consistent over time. Both cohorts have information on frequency and severity of wheeze, which allowed us to assess whether differences in severity explained the tendency for phenotypes to persist. Although the two cohorts use different measures of severity, the relationships between these markers and phenotypes are similar in both cohorts.

Phenotype definitions were based entirely on parental reports of symptoms during the previous 12 months. Parental assessment may be unreliable not only for the presence of wheeze, but also for wheeze severity and the presence of viral infections. In both cohorts, we defined phenotypes indirectly based on individual triggers of wheeze reported. Non-viral triggers may have been under-reported because not all possible triggers were specifically listed as response options in the questionnaires. However, in the LRC, parents' direct assessment of children's wheezing pattern shows good agreement with our phenotype definitions and does not suggest under-reporting of non-viral triggers (supplementary table S8). EVW may have been under-reported in ALSPAC, as wheeze with colds was not an explicit response option (table 1). This may explain the larger proportion of non-classifiable wheeze in ALSPAC. Although both cohorts were large and population-based, not all children participated in each survey. The samples with information available at baseline and follow-up were thus somewhat reduced and not fully representative of the entire cohorts.

How do the results compare with those of other studies?

Our study is the largest study to investigate the temporal stability of MTW and EVW and the only one to statistically test whether these phenotypes have a tendency to persist. Furthermore, it is the only study to investigate whether this phenotype persistence is explained by symptom severity – a known risk factor for the persistence of wheeze. To our knowledge, only four studies have assessed the stability of EVW and MTW over time [22, 23, 26, 27], and in these, the study populations were smaller than in either of our two cohorts. The results of these studies are summarised in supplementary table S9. Despite differences in study population and design, the proportions of children becoming asymptomatic or changing phenotype were broadly comparable to those in our study. Two of the four studies investigated both EVW and MTW, and one showed – in agreement with ours – that the proportion of children remaining in the same phenotype was larger for MTW than for EVW [22], while the other study showed greater stability for EVW [23]. However, none of these studies used regression modelling to investigate the tendency of phenotypes to persist or the extent to which such a tendency might be explained by symptom severity.

Our observation that the proportion of children with MTW increases with age while EVW decreases with age is in line with the findings of other studies [3, 6, 11, 28, 29]. An early cross-sectional study showed a positive correlation between age and allergy and exercise as triggers of asthma, and a negative correlation between age and respiratory infections [28]. Using partly overlapping data from the LRC, we have previously shown a decrease in the proportion of infections as an exclusive trigger among children with current wheeze, from 57% at age 1 to 21% at age 9 years, while the proportion of children also reporting other triggers increased correspondingly [29].

Similarly, our findings that MTW is associated with more severe wheeze than EVW confirm findings from other studies [6, 30]. Cross-sectional surveys in Aberdeen reported less frequent episodes, and less frequent night cough, shortness of breath and chest tightness in children with EVW than in those with MTW [6, 30].

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Interpretation

In both cohorts, we found that RRRs for EVW at follow-up were higher for children with EVW than for those with MTW at baseline, while RRRs for MTW at follow-up were higher for children with MTW at baseline. In the absence of any phenotype stability, we would have expected these RRRs to be equal. Instead, we found that children tend to remain in the same phenotype. We then explored whether this could be explained by differences in severity. If children with MTW on average had more severe disease, children classified as MTW at baseline would tend to be reclassified as MTW at follow-up. This did, in fact, explain part of the difference; however, the direction of our findings (higher RRRs for the same phenotype) remained the same after adjusting for severity. It is possible that results are still residually confounded by unmeasured severity. Although we corrected for a wide range of measures including frequency of episodes, shortness of breath, sleep and activity disturbance, these measures were based on parental reports and may be inaccurate. We also cannot exclude the possibility that the observed stability of phenotypes was partially due to the parents' tendency to give the same, possibly inaccurate, answers to the same questions on symptoms over time.

It should be noted that the stability of MTW observed in our study is not an artefact of its definition: it might, for instance, be objected that a child by definition becomes (and remains) a multitrigger wheezer from the first time they wheeze in response to a non-viral trigger. However in our study, children were assigned to phenotypes based only on triggers of wheeze in the previous 12 months. Thus, children who wheezed only with colds during this period were classified as EVW regardless of whether they had previously had MTW. This 12-month period of observation makes sense because interval symptoms may be seasonal and a classification based on shorter periods might be strongly affected by season.

Also, our study shows that EVW in preschool children should not be equated with early transient wheeze. Indeed, after adjustment, EVW had a similar predictive value for later wheeze as MTW, particularly in the ALSPAC cohort (supplementary table S4).

We suspect that our finding may be due to the fact that differences in the underlying disease processes – other than severity – cause some children to wheeze only during respiratory tract infections and others to be sensitive to other triggers. This reopens the possibility that certain therapies might indeed be more effective in certain phenotypes [9, 14, 16, 17]. More research is needed to understand the underlying differences between EVW and MTW. Epidemiological studies should continue to distinguish between these phenotypes and better characterise them regarding risk factors and prognosis. While translating such knowledge to clinical management will take time, our study suggests that we should not prematurely discard these phenotypes.

Conclusions

Using data from two large population-based birth cohorts, we found that MTW, and to a lesser extent EVW, shows a tendency to persist from preschool to early-school age. While many children in both phenotypes become asymptomatic, those that continue to wheeze tend to remain in the same phenotype, though some phenotype switching does occur. The tendency to remain in the same phenotype was only partially explained by wheeze severity, suggesting that there are other differences in the underlying disease processes of children with MTW and EVW.

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Table S1 : Questions used to assess severity of wheeze and definition of severity indicators

ALSPAC	LRC
Wheeze severity: 1) In the past year has she/he had any periods when there was wheezing with whistling on his chest when he breathed? i. Yes ii. No b. How many separate times has this happened in the past 12 months? i. Once ii. Twice iii. 3-4 times iv. 5 or more times c. Was she/he breathless during any of these times? i. Yes for all ii. Yes for some iii. No not at all d. How often, on average, has your child's sleep been disturbed due to wheezing in the past 12 months? i. Never woken with wheezing ii. Less than one night per week iii. One or more nights per week e. Has wheezing ever been severe enough to limit your child's speech to only one or two words at a time between breaths in the past 12 months? i. Yes ii. No	**Wheeze severity:** 1) How many attacks of wheezing has your child had during the last 12 months? i. None ii. 1 to 3 iii. 4 to 12 iv. More than 12 2) Do these attacks cause him/her to be short of breath? (only asked in 1999) i. Yes, always ii. Yes, occasionally iii. No, never 3) In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing? i. Never woken with wheezing ii. Less than one night per week iii. One or more nights per week 4) In the last 12 months, how much did wheezing interfere with your child's daily activities? i. Not at all ii. A little iii. A moderate amount iv. A lot
Definition of severity indicators: Frequent attacks: 1.b.iii or 1.b.iv (≥3 attacks) Shortness of breath: 1.c.i or 1.c.ii	**Definition of severity indicators:** Frequent attacks: 1. iii or 1.iv (≥4 attacks) Shortness of breath: 2.i or 2.ii

Sleep disturbance: 1.d.ii or 1.d.iii Speech limitation: 1.e.i	Sleep disturbance: 3.ii or 3.iii Interference with activities: 4.ii, 4.iii, or 4.iv

Table S2: Characteristics of children excluded and included from analyses

Characteristics	Not included in analyses		Included in analyses*				
	No surveys		1-2 surveys†		All 3 surveys‡		P
	n/N	%	n/N	%	n/N	%	
ALSPAC	**N=2950**		**N=3641**		**N=7468**		
Sex male	1506/2938	51.3	1916/3641	52.6	3844/7468	51.5	0.445
Ethnicity white	1689/1863	90.7	3174/3329	95.3	7181/7344	97.8	<0.001
Maternal smoking during pregnancy	979/2539	38.6	1149/3553	32.3	1542/7445	20.7	<0.001
Older siblings (≥1)	374/620	60.3	1805/3062	58.9	3973/7212	55.1	<0.001
Crowding, >1 person/room	177/480	36.9	822/2619	31.4	1480/6823	21.7	<0.001
Pet ownership	283/495	57.2	1599/2745	58.3	3894/7101	54.8	0.008
LRC	**N=1037**		**N=1843**		**N=1420**		
Sex male	531/1037	51.2	928/1843	50.4	764/1420	53.8	0.138
Ethnicity white	739/1037	71.3	1494/1843	81.1	1267/1420	89.2	<0.001
Maternal smoking during pregnancy	138/457	30.2	300/1474	20.4	160/1391	11.5	<0.001
Older siblings (≥1)	315/453	69.5	968/1437	67.4	869/1361	63.9	0.039
Crowding, >1 person/room	253/464	54.5	666/1472	45.2	484/1380	35.1	<0.001
Pet ownership	173/466	37.1	623/1495	41.7	603/1408	42.8	0.095

Abbreviations: ALSPAC Avon Longitudinal Study on Parents and Children, LRC Leicestershire Respiratory Cohort 1998-b

* Information on wheeze from at least on survey at age 2, 4, or 6 years

† Number of surveys (age 2, 4, or 6 years) from which information on wheeze was available

‡ P-values from χ^2-tests

Table S3: Characteristics of children at age 2 years according to phenotype of wheeze

Characteristics	EVW		MTW		NCW		P*
	n/N	%	n/N	%	n/N	%	
ALSPAC	**N=752**		**N=928**		**N=122**		
Sex male	440/752	58.5	559/928	60.2	70/122	57.4	0.698
Ethnicity white	724/734	98.6	844/884	95.5	114/116	98.3	<0.001
Maternal smoking during pregnancy	192/749	25.6	298/915	32.6	43/121	35.5	0.003
Older siblings (≥1)	439/708	62.0	522/850	61.4	64/111	57.7	0.682
Crowding, >1 person/room	144/655	22.0	251/799	31.4	45/98	45.9	<0.001
Pet ownership	395/682	57.9	479/832	57.6	51/103	49.5	0.262
LRC	**N=229**		**N=295**		**N=9**		
Sex male	134/229	58.5	181/295	61.4	2/9	22.2	0.058
Ethnicity white	203/229	88.6	259/295	87.8	8/9	88.9	0.954
Maternal smoking during pregnancy	35/220	15.9	69/292	23.6	2/9	22.2	0.099
Older siblings (≥1)	145/217	66.8	192/283	67.8	6/9	66.7	0.970
Crowding, >1 person/room	95/222	42.8	135/286	47.2	4/9	44.4	0.612
Pet ownership	98/227	43.2	107/293	36.5	2/9	22.2	0.176

Abbreviations: ALSPAC Avon Longitudinal Study on Parents and Children, LRC Leicestershire Respiratory Cohort 1998-b, EVW episodic viral wheeze, MTW multiple trigger wheeze, NCW Non-classifiable wheeze

* P-values from c^2-tests

Table S4: Association between wheeze phenotypes and wheeze 2 years later

Age at Baseline (years)	Age at Follow-up (years)	Phenotype at baseline	Current wheeze at follow up		
			n (%)	Crude OR (95% CI)	Adj. OR* (95% CI)
ALSPAC					
2	4	No wheeze	681 (10.3)	1	1
		EVW	301 (47.2)	7.8 (6.5, 9.3)	3.7 (2.9, 4.6)
		MTW	448 (59.0)	12.5 (10.6, 14.8)	4.4 (3.5, 5.7)
4	6	No wheeze	348 (5.4)	1	1
		EVW	179 (40.6)	11.9 (9.5, 14.8)	3.4 (2.5, 4.7)
		MTW	435 (60.7)	26.6 (22.2, 32.1)	4.9 (3.5, 6.8)
LRC					
2	4	No wheeze	163 (11.1)	1	1
		EVW	56 (31.8)	3.7 (2.6, 5.3)	2.5 (1.6, 3.9)
		MTW	120 (55.3)	9.9 (7.2, 13.5)	4.0 (2.3, 7.1)
4	6	No wheeze	101 (6.9)	1	1
		EVW	36 (37.5)	8.1 (5.1, 12.8)	7.0 (4.1, 12.0)
		MTW	131 (61.5)	21.5 (15.3, 30.3)	13.6 (7.7, 24.0)

Abbreviations: ALSPAC Avon Longitudinal Study on Parents and Children, LRC Leicestershire Respiratory Cohort 1998-b, EVW episodic viral wheeze, MTW multiple trigger wheeze

* Adjusted for symptom severity at baseline (frequent attacks, shortness of breath, sleep disturbance, interference with activities and speech limitation

Table S5: Association between wheeze phenotypes at baseline and 2-year follow-up

Age at baseline (years)	Age at follow-up (years)	Phenotype at baseline	N* (100 %)	No wheeze at follow-up n (%)	EVW at follow-up n (%)	EVW at follow-up Crude RRR† (95% CI)	EVW at follow-up Adj. RRR†‡ (95% CI)	MTW at follow-up n (%)	MTW at follow-up Crude RRR†‡ (95% CI)	MTW at follow-up Adj RRR† (95% CI)
ALSPAC										
2	4	No wheeze	6465	5934 (91.8)	237 (3.7)	1	1	294 (4.6)	1	1
		EVW	591	337 (57.0)	126 (21.3)	9.4 (7.4, 11.9)	4.6 (3.3, 6.4)	128 (21.7)	7.7 (6.1, 9.7)	3.2 (2.3, 4.3)
		MTW	699	311 (44.5)	73 (10.4)	5.9 (4.4, 7.8)	2.2 (1.5, 3.3)	315 (45.1)	20.5 (16.8, 24.8)	6.2 (4.6, 8.4)
4	6	No wheeze	6271	6057 (96.6)	79 (1.3)	1	1	135 (2.2)	1	1
		EVW	392	262 (66.8)	79 (20.2)	23.1 (16.5, 32.3)	8.0 (4.9, 13.1)	51 (13.0)	8.7 (6.2, 12.3)	2.0 (1.2, 3.3)
		MTW	616	282 (45.8)	52 (8.4)	14.1 (9.8, 20.5)	3.3 (1.9, 6.0)	282 (45.8)	44.9 (35.4, 56.9)	6.7 (4.3, 10.4)
LRC										
2	4	No wheeze	1461	1301 (89.1)	60 (4.1)	1	1	100 (6.8)	1	1
		EVW	176	120 (68.2)	27 (15.3)	4.9 (3.0, 8.0)	4.1 (2.2, 7.5)	29 (16.5)	3.1 (2.0, 4.9)	1.8 (1.0, 3.2)
		MTW	216	97 (44.9)	23 (10.7)	5.1 (3.0, 8.7)	3.3 (1.4, 7.7)	96 (44.4)	12.9 (9.1, 18.2)	4.1 (2.1, 7.9)
4	6	No wheeze	1459	1360 (93.2)	28 (1.9)	1	1	71 (4.9)	1	1
		EVW	95	60 (63.2)	19 (20.0)	15.4 (8.1, 29.1)	15.5 (7.3, 32.9)	16 (16.8)	5.1 (2.8, 9.3)	4.0 (2.0, 8.0)
		MTW	213	82 (38.5)	14 (6.6)	8.3 (4.2, 16.4)	7.0 (2.6, 18.9)	117 (54.9)	27.3 (18.9, 39.6)	15.6 (8.3, 29.2)

Abbreviations: ALSPAC Avon Longitudinal Study on Parents and Children, LRC Leicestershire Respiratory Cohort 1998-b, EVW episodic viral wheeze, MTW multiple trigger wheeze, RRR relative risk ratio

* Numbers include only children with classifiable wheeze (see Table 1) or no wheeze at baseline and follow-up

† Results from multinomial regression analysis including non-classifiable wheeze (see Table 1) but results for this category are not reported here.

‡ Adjusted for symptom severity at baseline (frequent attacks, shortness of breath, sleep disturbance, interference with activities and speech limitation).

Table S6: Association between wheeze phenotypes at age 2 and wheeze at age 6 years

Phenotype at baseline	Current wheeze at follow up		
	n (%)	Crude OR (95% CI)	Adj. OR* (95% CI)
ALSPAC			
No wheeze	461 (7.7)	1	1
EVW	177 (30.5)	5.3 (4.3, 6.4)	2.4 (1.9, 3.2)
MTW	277 (42.3)	8.8 (7.3, 10.6)	2.9 (2.2, 3.9)
LRC			
No wheeze	105 (8.6)	1	1
EVW	44 (28.2)	4.2 (2.8, 6.2)	2.4 (1.4, 4.0)
MTW	78 (42.6)	7.9 (5.5, 11.2)	3.0 (1.5, 5.8)

Abbreviations: ALSPAC Avon Longitudinal Study on Parents and Children, LRC Leicestershire Respiratory Cohort 1998-b, EVW episodic viral wheeze, MTW multiple trigger wheeze

* Adjusted for symptom severity at baseline (frequent attacks, shortness of breath, sleep disturbance, interference with activities and speech limitation

Table S7: Association between wheeze phenotypes at age 2 and age 6 years

Phenotype at baseline	N* (100 %)	No wheeze at follow-up n (%)	EVW at follow-up n (%)	EVW at follow-up Crude RRR† (95% CI)	EVW at follow-up Adj. RRR†‡ (95% CI)	MTW at follow-up n (%)	MTW at follow-up Crude RRR† (95% CI)	MTW at follow-up Adj. RRR†‡ (95% CI)
ALSPAC								
No wheeze	5854	5539 (94.6)	108 (1.8)	1	1	207 (3.5)	1	1
EVW	532	403 (75.8)	63 (11.8)	8.0 (5.8, 11.1)	3.2 (2.0, 5.2)	66 (12.4)	4.4 (3.3, 5.9)	1.7 (1.2, 2.6)
MTW	585	378 (64.6)	34 (5.8)	4.6 (3.1, 6.9)	1.3 (0.7, 2.4)	173 (29.6)	12.2 (9.8, 15.4)	3.4 (2.3, 5.1)
LRC								
No wheeze	1212	1111 (91.7)	28 (2.3)	1	1	73 (6.0)	1	1
EVW	156	112 (71.8)	22 (14.1)	7.8 (4.3, 14.1)	4.6 (2.0, 10.3)	22 (14.1)	3.0 (1.8, 5.0)	1.6 (0.8, 3.2)
MTW	183	105 (57.4)	8 (4.4)	3.0 (1.3, 6.8)	1.4 (0.4, 4.9)	70 (38.2)	10.1 (6.9, 14.9)	3.6 (1.7, 7.7)

Abbreviations: ALSPAC Avon Longitudinal Study on Parents and Children, LRC Leicestershire Respiratory Cohort 1998-b, EVW episodic viral wheeze, MTW multiple trigger wheeze

* Numbers include only children with classifiable wheeze (see Table 1) or no wheeze at baseline and follow-up

† Results from multinomial regression analysis including non-classifiable wheeze (see Table 1) but results for this category are not reported here.

‡ Adjusted symptom severity at baseline (frequent attacks, shortness of breath, sleep disturbance, interference with activities and speech limitation).

Table S8: Association between the indirect classification of wheeze phenotypes used in analyses, and parent's direct classification* into episodic and chronic wheeze in the LRC at age 6 years

MTW and EVW defined as in Table 1.	Episodic wheeze* n	(Row %)	Chronic wheeze* n	Row %	Total n	Row %	P-value Fisher's exact test
Wheeze at 2 years							
EVW	226	(99)	3	(1)	229	(100)	<0.001
MTW	222	(77)	68	(23)	290	(100)	
Wheeze at 4 years							
EVW	153	(99)	2	(1)	155	(100)	<0.001
MTW	267	(80)	68	(20)	335	(100)	
Wheeze at 6 years							
EVW	76	(97)	2	(3)	78	(100)	<0.001
MTW	189	(78)	52	(22)	241	(100)	

* Based on parents' response to the following questions: "Which of these two descriptions fits best your child's wheeze? 1) My child has only short attacks of wheeze, for example with colds. In between these attacks, he/she does not normally wheeze. 2) My child wheezes always or a lot of the time. With colds he/she has attacks with more severe wheeze". Episodic and chronic wheeze are defined as responses 1 and 2 respectively.

Table S9: Studies on the stability of EVW and MTW

Study	Study population, age at baseline	Follow-up period	Phenotype definition	Baseline	Phenotype at follow-up*			Percentage among children with wheeze at follow-up†	
				N	no wheeze n (%)	EVW n (%)	MTW n (%)	EVW %	MTW %
Studies on the stability of EVW (N = number of children with EVW at baseline)									
Present study		2 years							
ALSPAC 2-4 years	Population-based cohorts, 2.5 years		EVW: Wheeze triggered by infection or bronchitis MTW: Wheeze triggered by smoke, weather, allergens, air pollution, other	591	337 (57)	126 (21)	128 (22)	126 (50)	128 (50)
ALSPAC 4-6 years				392	262 (67)	79 (20)	51 (13)	79 (61)	51 (39)
LRC 2-4 years	Population-based cohorts, 2 years		EVW: Wheeze during or soon after a cold. MTW: Wheeze without cold and wheeze triggered by ecercise, excitement, allergens	176	120 (68)	27 (15)	29 (17)	27 (48)	29 (52)
LRC 4-6 years				95	60 (63)	19 (20)	16 (17)	19 (54)	16 (46)
Kapelle 2012[1]	Treated for wheeze at hospital, 1.9 years (median)	Min. 2 years	EVW: Wheeze only during viral colds. MTW: Wheeze during viral colds as well as smoke, fog or allergens.	78	36 (47)	23 (29)	19 (24)	23 (55)	19 (45)
Topal 2013[2]	Children hospitalized for wheeze, 2 years (median)	20 months	EVW: Wheeze only by infections, no wheeze between. MTW: Wheeze triggered by colds as well as	236	91 (38)	108 (46)	37 (16)	108 (74)	37(26)

			allergens, smoke, exercise or weather						
Van Wonderen 2015[3]	Children visiting physician because of cough or wheeze, 2 years (median)	1 year	EVW: Wheeze with colds but not between colds, past 12 months. MTW: Wheeze with colds and also between, past 12 months						
Baseline to 12 mo				126	50 (40)	67 (53)	9 (7)	67 (88)	9 (12)
Baseline to 24 mo				126	86 (68)	33 (26)	7 (6)	33 (83)	7 (17)
Schultz 2009	Children diagnosed with asthma, 4 years (median)	1 year	EVW: Wheezing only during colds and not in the absence of colds. MTW: Wheeze in the absence of colds, irrespective of wheeze with colds	38	13 (34)	12 (32)	13(34)	12 (48)	13(52)
Studies on the stability of MTW (N = number of children with MTW at baseline)									
Present study		2 years							
ALSPAC 2-4 years	Population-based cohorts, 2.5 years		EVW: Wheeze triggered by infection or bronchitis MTW: Wheeze triggered by smoke, weather, allergens, air pollution, other	699	311 (45)	73 (10)	315 (45)	73 (19)	315 (81)
ALSPAC 4-6 years				616	282 (46)	52 (8)	282 (46)	52 (16)	282 (84)
LRC 2-4 years	Population-based cohorts, 2 years		EVW: Wheeze during or soon after a cold. MTW: Wheeze without cold and wheeze triggered by ecercise, excitement, allergens	216	97 (45)	23 (11)	96 (44)	23 (19)	96 (81)
LRC 4-6 years				213	82 (39)	14 (7)	117 (55)	14 (11)	117 (89)
Van Wonderen 2015[3]	Children visiting physician because of cough or	1 year	EVW: Wheeze with colds but not between colds, past 12 months. MTW: Wheeze with						

	wheeze, 2 years (median)		colds and also between, past 12 months						
Baseline to 12 mo				49	13 (27)	14 (29)	22 (45)	14 (39)	22 (61)
Baseline to 24 mo				49	24 (49)	14 (29)	11 (22)	14 (56)	11 (44)
Schultz 2009[4]	Children diagnosed with asthma, 4 years (median)	1 year	EVW: Wheezing only during colds and not in the absence of colds. MTW: Wheeze in the absence of colds, irrespective of wheeze with colds	71	11 (16)	22 (31)	38 (54)	22 (37)	38 (63)

* Numbers and percentage (parenthesis) of children with no wheeze, EVW, and MTW at follow-up among children with the given baseline phenotype (100%).

† Numbers and percentage (parenthesis) of children with EVW, and MTW at follow-up among children with the given baseline phenotype who continued to wheeze at follow-up (non-wheezers at follow-up excluded).

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10.2 Co-author publication: The limitations of cross-sectional data: perinatal risk factors for asthma

Ardura-Garcia C, **Pedersen ESL**, Goutaki M.

Letter to the editor

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Own contribution: Help draft the manuscript, submit manuscript, and proof read.

The limitations of cross-sectional data: perinatal risk factors for asthma

To the Editor:

The relationship between perinatal factors and lung function or development of asthma has been studied for decades and we have increasing evidence for the importance of early life factors for respiratory health in adulthood [1]. Pregnancies in adolescent and older women have implications for maternal and child health. The topic is relevant at present, as first-birth rates for women aged >35 years have increased exponentially [2]. A number of studies showed an association between maternal age and respiratory symptoms and asthma in childhood, suggesting that lung development might differ between children born to very young or very old mothers [3]. However, the evidence for longer lasting effects is scarce.

We read with great interest the paper by Gómez Real *et al.* [4] analysing the effect of maternal age on lung function and asthma in adulthood. The authors used data from 10 692 adults aged 25–55 years, participating in the European Community Respiratory Health Survey (ECRHS) II. They found that maternal age at delivery was associated with better lung function (forced expiratory volume in 1 s) and lower risk of asthma and respiratory symptoms in the adult offspring. Both associations were only found in female offspring. The authors concluded that results were unchanged after adjustment for a range of potential confounders.

The authors proposed pathophysiological mechanisms to explain their findings. However, the effect observed is relatively small for such a large cohort and sex specific, making a causal association more improbable. Conversely, the effect of maternal age on offspring asthma may be mediated through other intermediate factors. We commend the authors for adjusting their findings for as many confounders as were available from the data, including birth order, birthweight, maternal smoking during pregnancy, maternal education, maternal asthma, daycare attendance, living environment in childhood, smoking history and body mass index. However, taking the opportunity from this carefully performed analysis, we would like to open up discussion on factors that are relevant when designing future studies on the association of perinatal factors with asthma in the offspring.

Most of the information on confounders in the study by Gómez Real *et al.* [4] was obtained through a questionnaire completed by the adult offspring, some of whom were aged >50 years, which could lead to recall and reporting bias. The authors acknowledged the risk of bias concerning self-reported asthma outcomes and maternal smoking, the latter being differential in those with a very young mother. However, there is little discussion about whether reporting bias might be different in those who developed asthma compared to those who did not. It is easy to imagine how mothers of asthmatic adults are more prone to conceal their smoking habits during pregnancy compared to mothers of healthy adults.

There are several other perinatal factors that influence asthma risk, such as birth modality and gestational age. Caesarean sections and low gestational age are more common among older mothers [5], and have been shown to increase the risk of asthma in the child [6, 7]. Including these factors as confounders in the study by Gómez Real *et al.* [4] might therefore further decrease the odds ratio reported for the association between maternal age and offspring asthma. Irrespective of the effect, these factors should be taken into account when studying the effect of maternal age.

Another potential confounder or effect modifier is breastfeeding. It has been shown that breastfed children have a lower risk of developing asthma and better lung function [8]. Studies on maternal age and initiation and duration of breastfeeding showed controversial results [9, 10] and it is difficult to ascertain how its

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Adjusting for residual confounding when studying perinatal factors and offspring health can be difficult but it is very important for designing future studies http://ow.ly/H78y30kPxMZ

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inclusion in the analysis would affect the association between maternal age and offspring asthma. Considering this, breastfeeding is an important factor to be taken into account when studying perinatal factors associated with asthma.

A methodological issue to consider in similar future studies is that the participants in the study by Gómez Real *et al.* [4] were born over a broad period of time (nearly 30 years). Both asthma prevalence and maternal age have increased worldwide over past decades [11]. Therefore, we should also consider the generational effect when analysing factors related to asthma risk. Adjusting the results for the year in which the offspring was born could have been done easily with the available data, removing this potential source of confounding.

To conclude, while residual confounding should be thoroughly studied before drawing firm conclusions on the effect of maternal age on lung function and asthma in the offspring, the findings from the study by Gómez Real *et al.* [4] are highly relevant and novel. The effect of maternal age on lung function in the offspring and the differences observed by sex should now be studied in the existing birth cohorts studying asthma, to see if findings can be reproduced. Prospective studies with a broad range of objectively recorded perinatal factors may be able to shed more light on this important matter, given the current trend of delayed motherhood.

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10.3 Co-author publication: Do clinical investigations predict long-term wheeze? A follow-up of pediatric respiratory outpatients.

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Do clinical investigations predict long-term wheeze? A follow-up of pediatric respiratory outpatients

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Abstract

Introduction: The contribution of clinical investigations to prediction of long-term outcomes of children investigated for asthma is unclear.

Aim: We performed a broad range of clinical tests and investigated whether they helped to predict long-term wheeze among children referred for evaluation of possible asthma.

Methods: We studied children aged 6 to 16 years referred to two Swiss pulmonary outpatient clinics with a history of wheeze, dyspnea, or cough in 2007. The initial assessment included spirometry, fractional exhaled nitric oxide, skin prick tests, and bronchial provocation tests by exercise, methacholine, and mannitol. Respiratory symptoms were assessed with questionnaires at baseline and at follow-up 7 years later. Associations between baseline factors and wheeze at follow-up were investigated by logistic regression.

Results: At baseline, 111 children were examined in 2007. After 7 years, 85 (77%) completed the follow-up questionnaire, among whom 61 (72%) had wheeze at baseline, while at follow-up 39 (46%) reported wheeze. Adjusting for age and sex, the following characteristics predicted wheeze at adolescence: wheeze triggered by pets (odds ratio, 4.2; 95% CI, 1.2-14.8), pollen (2.8, 1.1-7.0), and exercise (3.1, 1.2-8.0). Of the clinical tests, only a positive exercise test (3.2, 1.1-9.7) predicted wheeze at adolescence.

Conclusion: Reported exercise-induced wheeze and wheeze triggered by pets or pollen were important predictors of wheeze persistence into adolescence. None of the clinical tests predicted wheeze more strongly than reported symptoms. Clinical tests might be important for asthma diagnosis but medical history is more helpful in predicting prognosis in children referred for asthma.

KEYWORDS

asthma, cohort, epidemiology, prognosis, respiratory, wheeze

1 | INTRODUCTION

Asthma is the most prevalent chronic respiratory disease in childhood and adolescence, which leads to many health care visits.[1-3] Its key symptoms are wheeze, cough, and difficulty breathing, but symptoms vary substantially between individuals and across ages.[1,2] Some children who present with asthma symptoms continue to have problems later in life, while others do not. Better knowledge of their individual prognoses might affect their follow-up and answer questions of parents in the clinics.[4-6] Assessing prognosis of asthma

symptoms from school age into adulthood and identifying children at high-risk of symptom persistence is challenging.[4]

Studies investigating prognosis of asthma or wheeze in school-aged children are conducted with either clinical asthma cohorts or symptomatic children of a population-based cohort.[7] Studies in clinical asthma cohorts have found that lower FEV_1 (forced expiratory volume in 1 second), asthma severity, senitization to indoor allergens, eczema, hay fever, skin test reactivity, and bronchial hyper-responsiveness were associated with asthma persistence.[8-10] Studies in population-based cohorts have found that wheeze persistence was predicted by frequent attacks of wheeze, female sex, sensitization to furred animals or house dust mites, rhinitis, and bronchial hyper-responsiveness.[11-16]

For clinical practice, two knowledge gaps remain. First, few studies have examined the prediction of long-term prognosis, but none have done this for school-aged children seen in outpatient clinics for possible asthma. Second, many tests are performed in clinics to diagnose these children, but it is unclear whether these tests predict prognosis more accurately than reported symptoms alone. We determined whether clinical tests in addition to reported symptoms help predict wheeze in adolescence in school-aged children referred for possible asthma.

2 | METHODS

2.1 | Study population and study design

Of the 124 children invited, 111 were recruited from the respiratory outpatient clinics of two pediatric hospitals in Switzerland, 84 from St. Gallen and 27 from Basel, who were eligible if they had been referred for evaluation of current wheeze, dyspnea, or cough. Children with a known chronic respiratory disease such as cystic fibrosis or primary ciliary dyskinesia, or a respiratory tract infection during 4 weeks before the visit were excluded. At baseline in 2007-2008, parents completed a questionnaire and children underwent a set of standardized clinical tests during two different visits within 1 week as part of the study protocol.[17,18] At follow-up, 7 years after baseline, in 2014 to 2015, we sent a questionnaire to the 12 to 23 year-old adolescents or young adults (from now on referred to as adolescents) (E-figure 1).

Ethical approval was obtained from the local Ethics committee and all parents gave informed consent during the first visit at baseline and by sending back the questionnaire at follow-up (EKSG 07/001).

2.2 | Baseline assessment

The parental questionnaire included ISAAC key questions[19] plus additional questions on type and triggers of respiratory symptoms, atopic symptoms, previous treatments and environmental exposures (Supporting Information questionnaire 1 [German, original] and 2 [English, translation]). The study physician reported clinical test results, final diagnosis, and prescribed medication in a uniform way. Physicians diagnosed the children after all clinical tests were done, taking into consideration medical history, clinical examination, and all test results. Vocal cord dysfunction was diagnosed based on medical history, physical examination, and normal expiratory curves in spirometry.

The baseline assessment consisted of two visits. At the initial baseline visit, children performed spirometry, fractional exhaled nitric oxide (FeNO) measurement, a skin prick test (SPT), bronchial provocation test (BPT) by exercise, and by methacholine. At the second baseline visit, children did a BPT by mannitol. All clinical tests were performed according to published guidelines.[20-24] A detailed description of the test procedures has been published elsewhere [17,18,25] and is included in the Supporting Information material (E-text). Lung function measurements were compared to reference values from Zapletal et al.[26] We considered the exercise test as positive in the event of a ≥15% decrease in the FEV_1 after the exercise challenge test, and the methacholine test as positive when the minimal dose causing a ≥20% decrease of FEV_1 was <1 mg (the provocation dose, PD 20). The mannitol dry powder challenge test was considered as positive when a 15% fall in FEV_1 was measured before a cumulative dose of 635 mg was reached, or when a 10% fall in FEV_1 between two doses was reached. FeNO was measured using the portable NIOX MINO device (Aerocrine, Sweden), and was considered as positive when FeNO was higher than 26 ppb.[18] We performed skin prick tests for birch, grass, mugwort, *Alternaria*, cat, house dust mites (*D. pteronysinus*), and positive and negative controls.[18] These allergens cover 95% of inhaled allergens in Switzerland.[27] The test was considered to be positive if any mean wheal diameter was ≥3 mm.

2.3 | Assessment at follow-up

The follow-up questionnaire was very similar to the baseline questionnaire, but the questions were addressed directly to the adolescents instead of their parents (Supporting Information questionnaire 3 [German, original] and 4 [English, translation]).

2.4 | Definitions of wheeze and frequent wheeze

We assessed wheeze at follow-up with the question, "Have you had a whistling sound in the chest in the last 12 months?" If a child had had more than three attacks of wheeze in the last 12 months, we considered the child to have had frequent wheeze.

3 | STATISTICAL ANALYSIS

We compared the participants with information at baseline and follow-up to those without follow-up information to test for selection bias, using the χ^2 test. The participants with information at baseline and follow-up were included in the analysis. We investigated the association between exercise-induced wheeze and a positive exercise test at baseline using the Fisher's exact test, and the Mann-Whitney-*U* test when looking at the association of reported exercise-induced wheeze and the fall of FEV_1% predicted during the exercise test. We investigated the association between symptoms (Table 1) and clinical

TABLE 1 Characteristics of the study population at baseline and follow-up (N = 85)

	Baseline		Follow-up	
Age, median (range)	12	(6-16)	18	(12-23)
Respiratory symptoms[a], n (%)				
Wheeze	61	(72)	39	(46)
More than three attacks of wheeze	27	(32)	30	(35)
Exercise-induced wheeze	54	(64)	47	(56)
Disturbed sleep due to wheeze	28	(33)	10	(13)
Difficulty breathing due to wheeze	22	(27)	42	(56)
Limited daily activities due to wheeze	39	(46)	32	(38)
Wheeze with colds	36	(42)	29	(34)
Wheeze without colds	48	(56)	36	(42)
Wheeze triggers				
Pollen	31	(36)	21	(26)
House dust	15	(18)	13	(16)
Pets	15	(18)	16	(21)
Night cough	37	(44)	22	(26)
Hay fever	42	(51)	46	(57)
Eczema, atopic dermatitis	25	(30)	18	(23)
Inhaled medication[b], n (%)				
Any	71	(85)	44	(52)
Short-acting β2-agonizts, alone	47	(55)	21	(25)
ICS + short-acting β2-agonizts	6	(7)	2	(2)
ICS + long-acting β2-agonizts	18	(21)	21	(25)

Abbreviation: ICS, inhaled corticosteroids.
[a]In the last 12 months.
[b]At baseline prescribed medication by the study physician and at follow up self-reported use of medication in the last 12 months.

TABLE 2 Results of clinical tests and final diagnosis at baseline

Clinical test results and diagnosis	Baseline N = 85	
Test results		
Skin prick test, positive n (%)	33	(39)
FeNO test, positive n (%)	35	(41)
Methacholine test (N = 78)		
Positive n (%)	59	(76)
Provocation dose in mg (IQR)[a]	0.14	(0.07-0.5)
Mannitol test (N = 82)		
Positive n (%)	23	(28)
Provocation dose in mg (IQR)[b]	635	(547-635)
Exercise test (N = 76)		
Positive n (%)	18	(24)
Fall FEV1 in % predicted (IQR)[c]	8	(4-13)
Spirometry % predicted (IQR)		
FEV_1	101	(91-109)
FVC	102	(91-110)
MEF75	90	(80-100)
MEF50	82	(66-94)
MEF25	67	(51-87)
Diagnosis, n (%)		
Asthma or episodic viral wheeze[d]	62	(73)
Cough not due to asthma	11	(13)
Vocal cord dysfunction	7	(8)
Functional symptoms / hyperventilation	4	(5)
Recurrent colds	1	(1)

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, inter quartile range.
[a]median (IQR) provocation dose for a fall of ≥20% in FEV_1 (PD-20).
[b]median (IQR) provocation dose for a fall of ≥15% in FEV_1 (PD-15).
[c]median (IQR) fall in FEV_1 during exercise.
[d]including chronic and exercise related asthma, episodic viral wheeze, and otherwise triggered episodic wheeze.

test results (Table 2) at baseline with any wheeze and frequent wheeze at follow-up using logistic regression, adjusting for sex and age. For comparison, we repeated the analysis including only children diagnosed with asthma (N = 62). We did not consider interactions or a multivariable model because of the sample size. We used STATA software (version 14; College Station, TX) to analyze the data.

4 | RESULTS

4.1 | Characteristics of the study population at baseline and at follow-up

Eighty-five (77%) of the 111 children who participated in the baseline study completed the follow-up questionnaire. The median age was 12 years at baseline (range 6-16) and 18 at follow-up (12-23); 60% (51/85) were male. Wheeze was reported by 61 (72%) at baseline, and 7 reported cough without wheeze, 12 (14%) reported exercise-related breathing problems and 5 (6%) reported allergic rhinitis. Among those with wheeze, 27 (44%) had more than three attacks during 12 months before the baseline visit (Table 1). Symptoms at baseline were very similar in children who did not take part in the follow-up (E-table 1 Supporting Information). Asthma medication was prescribed at the baseline visit for 71 (85%) children, of whom 47 (55%) received inhaled short-acting β2-agonists (SABA) alone, 6 received SABA and inhaled corticosteroids (ICS), and 18 received long-acting β2-agonists (LABA) and ICS. At follow-up, 39 (46%) participants reported wheeze of whom 30 had more than three attacks during the last year. At follow-up, 44 adolescents (52%) reported using inhalers, including 21 using SABA alone, 2 using SABA and ICS, and 21 using LABA and ICS (Table 1).

Table 2 shows the clinical test results and diagnoses at baseline. All tests were completed in at least 90% of the children. The main reason for not completing a BPT was exhaustion.[17,18] For the 78 children who completed the BPT by methacholine at baseline, the test was positive in 76% and the median provocation dose was 0.14 mg. Eighty-two completed the BPT by mannitol, of whom 28% tested positive. The median provocation dose was 635 mg. Of the 76 children who completed the BPT by exercise, the median fall of FEV_1 was 8% predicted. The test was positive (≥15% decrease in the

FEV_1) in 18 (24%) children. SPT was positive in 33 (39%) children and FeNO was positive in 35 (41%). Doctors diagnosed 62 (73%) children with asthma or episodic viral wheeze. The other children were mostly diagnosed with cough not due to asthma or vocal cord dysfunction.

At baseline, self-reported exercise-induced wheeze was associated with a positive exercise test ($P = 0.022$; E-table 2).

4.2 | Baseline factors associated with wheeze and frequent wheeze at follow-up

Four respiratory symptoms and one clinical test at baseline were associated with *any wheeze* at follow-up. Of the reported symptoms, frequent wheeze (>3 attacks) (OR, 2.86, 95% CI, 1.10-7.43), exercise-induced wheeze (3.07, 1.19-7.96), wheeze triggered by pets (4.22, 1.21-14.76), and wheeze triggered by pollen (2.78, 1.11-6.98) were associated with wheeze at follow-up. For the clinical tests, only a positive exercise test was significantly associated with wheeze 7 years later (3.20, 1.05-9.70). Results remained very similar after adjusting for age and sex (Table 3). When we repeated the analysis for children diagnosed with asthma (N = 62), we found mostly comparable results (E-table 3). However, associations tended to be less strong (lower odds ratios) in particular for exercise induced wheeze (1.79, 0.58-5.48) and positive exercise test (2.00, 0.63-6.39)

Two respiratory symptoms were associated with *frequent wheeze* at follow-up. These were exercise-induced wheeze (OR, 3.05; 95% CI, 1.07-8.67) and wheeze triggered by pets (3.79, 1.15-12.48; E-table 4). None of the clinical test results were associated with frequent wheeze at follow-up.

5 | DISCUSSION

Among school-aged children referred to a respiratory outpatient clinic for evaluation of wheeze, cough, or dyspnea, 46% reported wheeze 7 years later. Reported exercise-induced wheeze and wheeze triggered by pets or pollen at baseline predicted wheeze at follow-up. Of the clinical tests, only a positive exercise challenge test predicted wheeze at follow-up, but no more strongly than reported exercise-induced wheeze. When we repeated the analysis based on children with asthma only, associations were weaker, probably because the same characteristics that predicted

TABLE 3 Associations between baseline factors and wheeze at follow up

Baseline factors	Wheeze[b] at follow-up N = 39	No wheeze at follow-up N = 46	Unadjusted OR (95% CI)	Adjusted[c] OR (95% CI)
Symptoms[a], n(%)				
Wheeze	31 (79)	30 (65)	2.07 (0.77-5.54)	2.23 (0.80-6.21)
More than three attacks of wheeze	17 (44)	10 (22)	2.78 (1.08-7.15)	2.86 (1.10-7.43)
Exercise-induced wheeze	30 (77)	24 (52)	3.06 (1.19-7.85)	3.07 (1.19-7.96)
Disturbed sleep due to wheeze	16 (41)	12 (26)	1.97 (0.79-4.93)	2.23 (0.84-5.96)
Difficulty breathing due to wheeze	13 (34)	9 (20)	2.08 (0.77.5.61)	2.06 (0.76-5.60)
Wheeze with colds	18 (46)	18 (39)	1.33 (0.56-3.16)	1.41 (0.57-3.49)
Wheeze without colds	26 (67)	22 (48)	2.18 (0.90-5.27)	2.27 (0.92-5.60)
Wheeze triggered by allergens				
Pollen	19 (49)	12 (26)	2.69 (1.08-6.68)	2.78 (1.11-6.98)
House dust	8 (21)	7 (15)	1.44 (0.47-4.40)	1.43 (0.46-4.39)
Pets	11 (28)	4 (9)	4.12 (1.19-14.3)	4.22 (1.21-14.8)
Night cough	19 (49)	18 (40)	1.43 (0.60-3.39)	1.48 (0.60-3.67)
Hay fever	23 (62)	19 (41)	2.33 (0.96-5.67)	2.52 (1.00-6.31)
Eczema, atopic dermatitis	15 (38)	10 (22)	2.19 (0.84-5.68)	2.31 (0.87-6.13)
Clinical tests, n (%)				
Skin prick test, positive	16 (41)	17 (37)	1.19 (0.49-2.85)	1.20 (0.49-2.94)
FeNO test, positive	19 (49)	16 (35)	1.78 (0.74-4.27)	1.77 (0.74-4.28)
Methacholine test, positive	28 (80)	31 (70)	1.68 (0.59-4.80)	1.66 (0.58-4.77)
Mannitol test, positive	9 (20)	14 (38)	2.43 (0.91-6.54)	2.53 (0.92-6.93)
Exercise test, positive	11 (35)	7 (16)	2.99 (1.00-8.89)	3.20 (1.05-9.70)
Spirometry % pred. median (IQR)				
FEV_1	100 (16)	101 (12)	1.00 (0.97-1.03)	1.00 (0.97-1.03)
FVC	103 (15)	102 (11)	1.00 (0.97-1.04)	1.01 (0.97-1.04)

Abbreviation: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, inter quartile range.
[a]In the last 12 months.
[b]Wheeze is defined as having wheeze in the last 12 months.
[c]Adjusted for age and sex.

persistence (exercise induced wheeze, positive exercise test) had already been used by the clinicians to decide on a diagnosis of asthma.

A few studies have examined the prediction of prognosis by clinical testing, but ours is the only study to have done this for so many clinical tests in school-aged children referred to a respiratory outpatient clinic. We did not find an association between FEV_1 or bronchial provocation test by methacholine at baseline and wheeze 7 years later; previous studies have reported contradictory findings. Both the CAMP cohort of 909 children aged 5 to 12 years with diagnosed asthma and another Dutch clinical cohort study of 5 to 14 year-old children diagnosed with asthma found that asthma persistence at ages 15 to 20 and 32 to 42, respectively, was associated with decreased FEV_1 at school-age.[8,9] In contrast, the population-based Tasmanian cohort did not find an association between FEV_1 at age 7 and wheeze persistence at age 29 to 32.[15] The CAMP study also found that a lower methacholine provocation concentration was associated with asthma persistence from age 5 to 12 until age 15 to 20.[9] In contrast, the population based Dunedin cohort of 613 children reporting wheeze at age 9 and a Norwegian cohort of 62 children reporting asthma at age 10, found that bronchial provocation test by methacholine was not associated with persistence at age 26 and 16, respectively, which is in line with our findings.[12,28] The Norwegian cohort did not find bronchial provocation test by exercise to be associated with asthma persistence from age 10 to age 16, which is in contrast to the association we found.[28] This heterogeneity between studies could be because children with wheeze from population-based cohorts might have milder disease than those in clinical studies. FeNO was not associated with wheeze persistence in children aged 6 to 16 years old suspected for asthma in our study. In contrast, FeNO was reported to predict asthma in preschool children with wheeze.[29-32] To our knowledge, no studies assess the predictive value of FeNO on wheeze persistence at school age. Available publications assessed the predictive value of FeNO on asthma control, relapse or exacerbations in asthmatic children, but with a short follow-up.[33-36]

Our observation that frequent attacks of wheeze at school age predicted wheeze persistence 7 years later is in line with findings from the Melbourne and Tasmanian cohorts.[10,11] In contrast to their findings, we found no significant association between either eczema or hay fever at baseline and wheeze persistence. This could be because those cohorts used different outcomes—severe wheeze and atopic asthma, respectively—or simply because we had low numbers and limited power.

A possible limitation of our study was that the bronchial provocation tests were done within a short period of time. This could have influenced the methacholine test result, which was performed after the exercise test on the same day and was positive in 76% of the children. Most likely the bronchial provocation test by mannitol was not influenced by the short time interval. We assured an appropriate interval of at least 24 hours without a change in respiratory health or medication in this time interval. A second limitation was the small sample size, which limited statistical power and did not allow us to perform a multivariable analysis including all symptoms and test results simultaneously. Adolescents might have underreported respiratory symptoms, which might have led to an underestimation of the proportion of adolescents with wheeze. However, since this underreporting is not likely to be associated with symptoms or positive test results at baseline, this should not have influenced the results relating to risk factors.

The main strength of our study is its clinical design, which reflects the typical mix of patients in a pediatric outpatient clinic. All children were first-time referrals to the pediatric respiratory clinic for evaluation of possible asthma. Therefore, the study population is representative of daily clinical work, in contrast to many clinical studies that selectively include well-defined moderate to severe asthmatics and leave out patients with unclear degrees of airway reactivity. Our study also profited from a very detailed baseline examination. Children in the study had an extensive array of examinations for lung function, BPT, and allergy, which allowed us to assess the contribution of clinical tests in predicting long-term wheeze in addition to reported symptoms among those referred for evaluation of possible asthma.

6 | CONCLUSION

This study is an initial step towards finding out whether clinical tests can predict wheeze later in life. Though clinical tests might be important for asthma diagnosis, our results suggest that they do not strongly predict prognosis of wheeze. In contrast, our data underline the importance of a detailed history, as school-age children reporting exercise-related wheeze and wheeze triggered by allergens were at higher risk and thus might profit from more frequent follow-up.

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AUTHOR CONTRIBUTIONS

CK and JB conceptualized and designed the study. DT and JB supervised data collection. CdJ analyzed the data and drafted the manuscript. EP and MG supported the statistical analysis and gave input for interpretation of the data. All authors critically revised the manuscript and approved the final manuscript as submitted.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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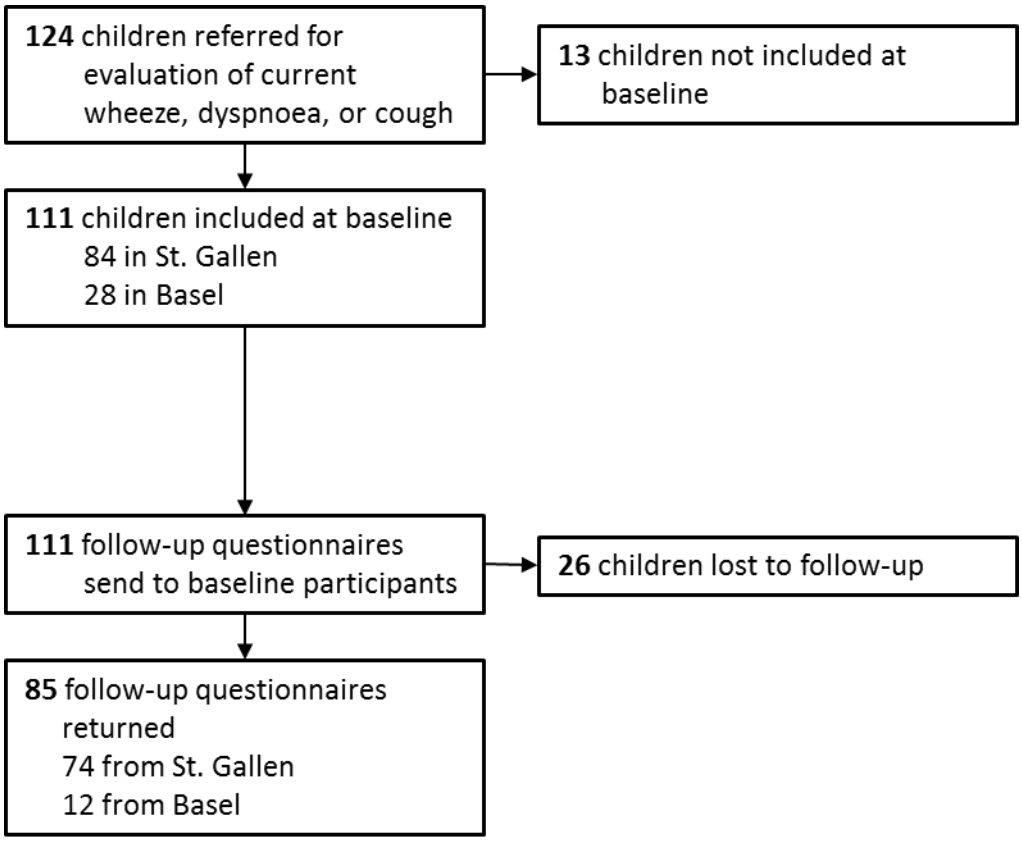
E-figure 1: Flowchart of patient recruitment at baseline and follow-up



E-table 1. Comparison of characteristics of the children included in the follow-up study and the children that did not take part in the follow-up study

Characteristics	**Complete information, Included** N=85		**No follow-up information, Not included** N=27		**p-value[d]**
Age, median (range)	12	(6-16)	11	(6-15)	0.269
Sex, male n(%)	8	(31)	34	(40)	0.396
Respiratory symptoms[a], n(%)					
Wheeze	61	(72)	19	(73)	0.896
More than 3 attacks of wheeze	27	(32)	11	(42)	0.321
Exercise-induced wheeze	54	(64)	16	(62)	0.854
Disturbed sleep due to wheeze	28	(33)	8	(31)	0.836
Difficulty breathing due to wheeze	22	(27)	3	(12)	0.113
Limited daily activities due to wheeze	39	(46)	12	(46)	0.981
Wheeze with colds	36	(42)	7	(26)	0.126
Wheeze without colds	48	(56)	19	(70)	0.199
Wheeze triggers					
Exercise	54	(64)	15	(56)	0.458
Laughing	11	(13)	5	(19)	0.471
Pollen	31	(36)	5	(19)	0.082
House dust	15	(18)	6	(22)	0.596
Pets	15	(18)	5	(26)	0.697
Food/drinks	3	(4)	0	(0)	0.322
Night cough	37	(44)	11	(42)	0.876
Hay fever	42	(51)	7	(27)	0.034
Eczema, atopic dermatitis	25	(30)	1	(4)	0.008
Parental smoking	23	(27)	8	(30)	0.795
Inhaled Medication[b], n(%)					
Any	71	(85)	15	(58)	0.004
Short-acting β2-agonists	47	(55)	7	(26)	0.008
ICS[c] + Short-acting β2-agonists	6	(7)	3	(11)	0.500
ICS[c] + Long-acting β2-agonists	18	(21)	5	(19)	0.766

[a] In the last 12 months

[b] At baseline prescribed medication by the study physician after the diagnostic tests and at follow up self-reported use of medication in the last 12 months

[c] Inhaled corticosteroids (ICS)

[d] chi-square test for dichotomous and t-test for continuous variables.

E-table 2 Association between reported exercise-induced wheeze and exercise test result at baseline N=76

Reported exercise-induced wheeze	**Exercise test** negative n(%column)[%row]	**Exercise test** positive n(%column)[%row]	**Total**
No	25 (43) [93]	2 (11) [7]	27
Yes	33 (57) [67]	16 (89) [33]	49
Total	58	18	

Fisher's exact: p-value 0.022

E-table 3 Associations between baseline factors and wheeze at follow up in children with diagnosed asthma

Baseline factors	**Wheeze** [b] **at follow up** N=30	**No wheeze at follow up** N=55	Unadjusted OR (95% CI)	Adjusted[c] OR (95% CI)
Symptoms[a]**,** n(%)				
Wheeze	26 (81)	22 (73)	1.58 (0.47-5.24)	1.62 (0.46-5.69)
More than 3 attacks of wheeze	16 (50)	9 (30)	2.33 (0.82-6.63)	2.46 (0.82-7.35)
Exercise-induced wheeze	24 (75)	18 (60)	2.00 (0.68-5.91)	1.79 (0.58-5.48)
Disturbed sleep due to wheeze	15 (47)	11 (37)	1.52 (0.55-4.21)	1.86 (0.60-5.76)
Difficulty breathing due to wheeze	12 (39)	6 (20)	2.53 (0.80-7.98)	2.40 (0.74-7.79)
Wheeze with colds	16 (50)	12 (40)	1.50 (0.55-4.11)	1.54 (0.54-4.41)
Wheeze without colds	22 (69)	17 (57)	1.68 (0.60-4.76)	1.69 (0.56-5.11)
Wheeze triggered by allergens				
Pollen	16 (62)	11 (41)	2.33 (0.77-7.00)	2.61 (0.79-8.58)
House dust	7 (29)	6 (23)	1.37 (0.39-4.88)	1.28 (0.35-4.71)
Pets	11 (41)	4 (15)	4.12 (1.12-15.3)	4.22 (1.10-16.2)
Night cough	15 (47)	14 (47)	1.01 (0.37-2.74)	1.01 (0.34-3.08)
Hay fever	19 (63)	14 (47)	1.97 (0.70-5.54)	2.28 (0.77-6.81)
Eczema, atopic dermatitis	13 (41)	7 (23)	2.25 (0.75-6.76)	3.31 (0.96-11.44)
Clinical tests, n(%)				
Skin Prick Test, positive	15 (47)	13 (43)	1.15 (0.42-3.14)	1.33 (0.46-3.83)
FeNO test, positive	18 (56)	15 (50)	1.29 (0.47-3.49)	1.08 (0.38-3.07)
Methacholine test, positive	25 (86)	27 (93)	0.46 (0.08-2.75)	0.36 (0.06-2.22)
Mannitol test, positive	14 (47)	9 (31)	1.94 (0.67-5.64)	1.90 (0.63-5.70)
Exercise test, positive	11 (39)	7 (23)	2.13 (0.68-6.62)	2.00 (0.63-6.39)
Spirometry % pred. median(IQR)				
FEV_1	100 (17)	98 (14)	1.00 (0.97-1.04)	1.00 (0.97-1.04)
FVC	102 (15)	102 (11)	1.00 (0.96-1.03)	0.99 (0.96-1.03)

IQR=inter quartile range

[a] In the last 12 months

[b] Wheeze is defined as having wheeze in the last 12 months

[c] Adjusted for age and sex

E-table 4 Associations between baseline factors and frequent wheeze at follow up

Baseline factors	**Frequent[b] wheeze at follow up** N=30	**No frequent wheeze at follow up** N=55	Unadjusted OR (95% CI)	Adjusted[c] OR (95% CI)
Symptoms[a], n(%)				
Wheeze	24 (80)	37 (67)	1.95 (0.68-5.60)	1.88 (0.62-5.68)
More than 3 attacks of wheeze	12 (40)	15 (27)	1.78 (0.69-4.56)	1.74 (0.66-4.57)
Exercise-induced wheeze	23 (77)	31 (56)	2.54 (0.94-6.91)	3.05 (1.07-8.67)
Disturbed sleep due to wheeze	12 (40)	16 (29)	1.63 (0.64-4.13)	1.44 (0.53-3.87)
Difficulty breathing due to wheeze	10 (34)	12 (22)	1.84 (0.68-5.00)	2.10 (0.74-5.91)
Wheeze with colds	15 (50)	21 (38)	1.62 (0.66-3.98)	1.49 (0.57-3.86)
Wheeze without colds	19 (63)	29 (53)	1.55 (0.62-3.85)	1.58 (0.61-4.05)
Wheeze triggered by allergens				
Pollen	13 (43)	18 (33)	1.57 (0.63-3.93)	1.50 (0.59-3.83)
House dust	3 (10)	12 (22)	0.40 (0.10-1.54)	0.40 (0.10-1.59)
Pets	9 (30)	6 (11)	3.50 (1.11-11.1)	3.79 (1.15-12.5)
Night cough	17 (57)	20 (37)	2.22 (0.90-5.52)	2.16 (0.82-5.67)
Hay fever	19 (66)	23 (43)	2.56 (1.00-6.53)	2.31 (0.88-6.00)
Eczema, atopic dermatitis	10 (33)	15 (28)	1.30 (0.50-3.41)	1.19 (0.44-3.21)
Clinical tests, n(%)				
Skin Prick Test, positive	13 (43)	20 (36)	1.34 (0.54-3.32)	1.32 (0.51-3.39)
FeNO test, positive	13 (43)	22 (40)	1.15 (0.47-2.83)	1.27 (0.50-3.23)
Methacholine test, positive	21 (75)	38 (75)	1.68 (0.59-4.80)	1.10 (0.37-3.25)
Mannitol test, positive	10 (36)	13 (24)	1.75 (0.65-4.73)	1.93 (0.69-5.41)
Exercise test, positive	8 (31)	10 (20)	1.78 (0.60-5.25)	1.96 (0.65-5.95)
Spirometry % pred. median(IQR)				
FEV_1	100 (15)	101 (13)	1.00 (0.97-1.03)	1.00 (0.97-1.03)
FVC	106 (13)	101 (13)	1.01 (0.98-1.05)	1.01 (0.98-1.05)

IQR=inter quartile range

[a] In the last 12 months

[b] Frequent wheeze is defined as having more than 3 attacks of wheeze in the last 12 months

[c] Adjusted for age and sex

Supplementary text:
Methods of clinical tests

Children withheld short acting beta$_2$-agonists for 8 hours, inhaled corticosteroids, leukotriene antagonists, and long acting beta$_2$-agonists for 24 hours, and antihistamines and sodium cromoglycate for >72 hours.

Spirometry
Spirometry was performed using ATS criteria for paediatric lung function testing [1] and a Jaeger masterscope (Erich Jaeger GmbH, Würzburg, Germany), using JLAB software, version 4.34. Spirometry was done in duplicate and the highest of these measures was recorded. Reference for prediction of lung function measurements were based on Zapletal et al. [2]

FeNO measurement
We measured FENO in doublets before spirometry, using the portable multi-gas analyser (NIOX MINO®, Aerocrine, Sweden), in accordance with published guidelines[3] and previous studies using this device.[4,5] The portable analyser ensures a constant expiratory flow of 50±5 ml/s, has an accuracy of ±10% with a minimum of ±5 ppb. FENO measurements from this portable analyser correlate well with those obtained by chemiluminiscence detectors.[5]

Skin prick test
We performed skin prick tests using birch, grass, mugwort, alternaria, cat, house dust mites (D. pteronyssinus), and positive and negative controls, considering a wheal of >3 mm as positive. These allergens cover 95% of inhaled allergies in Switzerland.[6]

Bronchial provocation test

- **Exercise challenge test**

The children performed the exercise challenge using a treadmill (T-2100, GE Healthcare, Freiburg, Germany) or a bicycle ergometer (ER Ergoselect 200, Ergoline GmbH, Bitz, Germany) for 8 min, inspiring room air according to published ATS and ERS guidelines.[7,8] At one site, children chose between treadmill and bicycle, at the other only a treadmill was available. We performed exercise testing under controlled conditions (maintaining inspired air temperature at 20–25°C and humidity of <10 mg water/L) [9] and measured heart rate and oxygen saturation by pulse oximeter with a forehead sensor (Nellcor N595 OxiMax, Tyco Healthcare, Neustadt/Donau, Germany). After baseline spirometry we started exercise testing at 60% target workload (defined as Watt = measured FEV_1 x 53.76-11.07), rapidly increasing workload aiming at 75% of the target in the second minute, 90% in the third minute, and 100% in the fourth minute, sustaining the latter for ≥4 min. We increased workloads more rapidly if the heart rate was not expected to reach at least 85% of the predicted maximum (220-age in years).[7] Spirometry was performed 1, 3, 5, 7, 10, and 15 min after exercise, in duplicate,[10] using a Jaeger masterscope (Erich Jaeger GmbH, Würzburg, Germany, with JLAB software version 4.52.0). If lung function had not returned to baseline after 15 min or in case of dyspnea, children received a short-acting beta2-agonist (salbutamol pMDI 100 μg 2–4 puffs via spacer). Exclusion criteria for exercise testing were significant airflow obstruction (FEV_1 ≤65%) at baseline and unwillingness to cooperate. A fall of FEV_1 ≥15% was considered as positive.[7] Reference for prediction of lung function measurements were based on Zapletal et al.[2]

- **Methacholine challenge test**

The children performed the methacholine challenge based on the Five-Breath Dosimeter Protocol. [7,9] They first inhaled NaCL 0.9% as a baseline value, then they inhaled stepwise 0.05mg, 0.05mg, 0.2mg, 0.3mg, 0.6mg and 1.2mg (cumulative dose of 2.4 mg in children <14 years old) via a nebulizer. Children older than 14 years old had an additional inhalation step with a cumulative dose of 3.2mg methacholine.
At end exhalation during tidal breathing, the children inhaled slowly and deeply from the nebulizer. The dosimeter is triggered after the inhalation begins, and the subject is encouraged to continue inhaling slowly and to hold the breath for another 5 seconds. This step is repeated for a total of five inspiratory capacity inhalations which should not take more than 2 minutes. The challenge is terminated when the FEV_1 falls by 20% or more, or the highest dose is given. Lung function was measured in 5-min intervals until it had returned to within 5% of the baseline value. If there was no return to base level after 30 min, salbutamol 200 mcg (two puffs Ventolin1 pMDI via spacer) was given to reverse the bronchoconstriction.
The results of the Methacholine challenge test are reported as percent decrease of FEV_1 from baseline, and PD20 is calculated.

- **Mannitol dry powder challenge test**

The protocol recommended by Anderson et al. [11] was followed, with slight modifications. Baseline FEV_1 was measured in triplicate and the highest of these measures was recorded. The measurement of FEV_1 was made using ATS criteria for pediatric lung function testing [1] and a Jaeger masterscope (Erich Jaeger GmbH, Würzburg, Germany), using JLAB software, version 4.34. Subjects were excluded from the challenge if their baseline FEV_1 was less than or equal to 65% of predicted.
Gelatine capsules (Gallipot, St. Paul, MS) were hand filled with 5, 10, 20 ($\pm$0.2), and 40 ($\pm$0.5) mg of MDP, using an analytical balance (Mettler AE200, Greifensee, Switzerland). The filled capsules were stored in dry conditions, using an airtight container that contained silica gel. [11,12]

Before the children were asked to inhale MDP, we assessed peak inspiratory flow through the dry powder delivery device (Inhalator, Boehringer, Ingelheim, Germany) which was attached to the spirometer (Jaeger Masterscope). A minimum of 30 l/min was required to continue the study.
The children were then asked to inhale the contents of an MDP capsule through the delivery device. The following schedule was used: 0 mg (empty capsule acting as a placebo), or initial doses: 5, 10, 20, 40, 80, 160, 160, and 160 mg. The doses of 80 mg and above were achieved by administering multiples of either 20-mg or 40-mg capsules.
Sixty seconds after inhalation, the subject had two measurements of lung function performed. The higher value from these two expiratory maneuvers was recorded. The FEV_1 value measured after the 0-mg capsule was used as baseline (pre-FEV_1) to calculate the percent decrease in FEV_1 in response to the mannitol challenge. If the subject had a decrease >10%, then the dose producing this was repeated for safety reasons. The percent fall in FEV_1 was calculated using the following formula: % Fall Index 1⁄4 [(pre-FEV_1 – post-FEV_1)/pre-FEV_1] x 100. This process was repeated until either the lung function (FEV_1) had fallen by 15% or the subject had reached the maximum dose (cumulative dose of 635 mg mannitol). A % Fall Index of 15% or greater was considered a positive response. It is the

standard to consider a 15% fall in FEV_1 as positive, as it represents approximately twice the coefficient of variation of the FEV_1 measurement. In addition, the log (post-FEV_1/pre-FEV_1) and the PD15 for mannitol were calculated from the relationship between the % fall in FEV_1 and the cumulative dose of mannitol required to provoke this.
Lung function was measured in 5-min intervals until it had returned to within 5% of the baseline value. If there was no return to base level after 30 min, salbutamol 200 mcg (two puffs Ventolin® pMDI via spacer) was given to reverse the bronchoconstriction.

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10.4 Co-author publication: Does high-flow oxygen reduce escalation of care in infants with hypoxemic bronchiolitis?

Mozun R, **Pedersen ESL**, Ardura-Garcia C.

Commentary

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Journal club

Does high-flow oxygen reduce escalation of care in infants with hypoxaemic bronchiolitis?

Commentary on:

Franklin D, *et al*. A randomised trial of high-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med* 2018; 378:1121–1131.

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Context

Bronchiolitis is an acute, lower respiratory tract disease of viral aetiology that affects infants below 2 years of age [1]. Bronchiolitis is common. One in five children have at least one healthcare visit related to bronchiolitis during infancy and it is a major cause of hospitalisation, accounting for 18% of all hospitalisations in the USA in children younger than 1 year [2]. The diagnosis is clinical and based on viral respiratory infection symptoms and signs such as tachypnoea, wheeze, crackles, rhonchi and respiratory distress [3]. There are no effective medical therapies for bronchiolitis so treatment is based on hydration and respiratory supportive care when necessary [3]. The use of high-flow oxygen through nasal cannula as respiratory support in infants with bronchiolitis has increased in recent years [4]. It provides a high flow of humidified air warmed to body temperature with an adjustable fraction of oxygen, and is usually well tolerated by infants. It may improve oxygenation and breathing effort by producing a positive pressure at the end of the expiration [5]. Franklin *et al*. [6] examined treatment failure resulting in escalation of care in infants with bronchiolitis and hypoxaemia who were treated in emergency departments or general paediatric wards with either high-flow oxygen or standard therapy with supplemental oxygen through a nasal cannula.

Methods

This multicentre randomised controlled trial was conducted in 17 Australian and New Zealand hospitals; eight of the hospitals had an on-site intensive care unit (ICU). Infants younger than 12 months presenting with signs of bronchiolitis and needing supplemental oxygen to keep oxygen saturation above 92% or 94%, depending upon institutional practice, were included. Infants who needed oxygen therapy for any reason other than suspected bronchiolitis were excluded. Eligible infants were randomised to receive either standard-therapy oxygen through a nasal cannula up to a maximum flow of 2 L·min^{-1}, or high-flow therapy with humidified air with variable oxygen through a nasal cannula at a rate of 2 L·min^{-1} per kilogram bodyweight. In the standard-therapy group, flow rate was adjusted, while in the high-flow group the inspiratory oxygen fraction (FIO_2) was varied. In both groups this was done to maintain oxygen saturation in the range of 92–98% (six hospitals) or 94–98% (11 hospitals). Children were randomised using a

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Treatment failure leading to escalation of care occurred less often in infants with hypoxaemic bronchiolitis treated with high-flow oxygen than with standard oxygen therapy, but there were no differences in the proportion needing ICU transfer or intubation http://bit.ly/2F3rSi1

computer-generated randomisation sequence with a block size of 10, stratified by hospital. Allocation was concealed but treatment was not blinded. The primary outcome was treatment failure resulting in an escalation of care. A conclusion of treatment failure was reached by a clinician if at least three of four criteria were met: 1) heart rate remained unchanged or increased since admission; 2) respiratory rate remained unchanged or increased since admission; 3) oxygen requirement in the high-flow group exceeded a F_{IO_2} of at least 0.4 to maintain an oxygen-saturation level of at least 92% or 94%, depending on hospital threshold, or the requirement for supplemental oxygen in the standard-therapy group exceeded 2 $L \cdot min^{-1}$ to achieve the same oxygen-saturation threshold; 4) the hospital internal early-warning tool (a standardised set of physiological and clinical factors) indicated medical review and escalation of care. Clinicians could also escalate care if they considered it appropriate for other clinical reasons apart from the four explicit criteria. Escalation of treatment was defined as an increase in respiratory support. Infants in the standard-therapy group who required escalation of care were changed to high-flow oxygen therapy and infants in the high-flow group were transferred to an ICU. Secondary outcomes included the proportion of children transferred to an ICU; intubation; durations of hospital stay, ICU stay and oxygen therapy; and adverse events.

Main results

Between October 2013 and August 2016, 2217 infants were eligible for inclusion, 1638 (74%) underwent randomisation, and 1472 (90% of those randomised) were included in the analysis. Treatment failure leading to escalation of care occurred more often in the standard-therapy group (167 out of 733, 23%) than in the high-flow therapy group (87 out of 739, 12%) with a risk difference of 11% (95% CI 7–15%). Escalation of care was influenced by whether the hospital had an on-site ICU. In hospitals without an on-site ICU, care was escalated in 69 out of 247 infants (28%) in the standard-therapy group and 20 out of 270 (7%) in the high-flow group. In hospitals with an on-site ICU, care was escalated in 98 out of 486 infants (20%) in the standard-therapy group and 67 out of 469 (14%) in the high-flow group. Restricting analysis to children meeting at least three of the four criteria, treatment failure remained lower in the high-flow group, in which 53 out of 739 (7%) infants experienced treatment failure, in comparison with 115 out of 733 (16%) in the standard-therapy group. There was no difference between the high-flow and the standard-therapy group regarding any of the secondary outcomes.

Commentary

This randomised controlled trial showed that treatment failure leading to escalation of care among children admitted for hypoxaemic bronchiolitis was lower among infants treated with high-flow oxygen supplementation than those treated with standard therapy. However, certain aspects of the study suggest that its results should be interpreted with caution. Comparison of the two groups is complicated by different main outcome definitions. In the high-flow oxygen group, the only way to escalate care was to transfer to ICU, whereas escalation of care in the standard-therapy group was to cross over and start high-flow oxygen. Clinicians might perceive switching infants from standard nasal cannula to high-flow oxygen as a smaller escalation step than transferring infants under high-flow oxygen therapy to the ICU, especially if high-flow therapy was already standard practice in their hospital. Were this true, it would increase escalation of care in the standard-therapy group compared to the high-flow group. Infants in the standard-therapy group had a lower respiratory rate at escalation than infants in the high-flow oxygen group, which suggests that perception was, to some extent, present. To address this problem, the authors performed a sensitivity analysis using the sample of patients that strictly met at least three out of four preset criteria for escalation of care. The analysis showed that escalation of care remained higher in the standard-therapy group, indicating that high-flow oxygen might really be better than standard therapy.

Presence or absence of an on-site ICU affected the risk of escalation of care in a different way in each treatment group. The risk difference in escalation of care was greater in hospitals without an on-site ICU than in those with an ICU. Possible reasons for this differ. ICU patient transfer could have been easier in hospitals with an on-site ICU. Also, clinicians might have greater confidence in waiting to escalate care from standard-therapy to high-flow oxygen if an ICU was present on-site. Therefore, it seems that mode of oxygenation did not alone influence escalation of care, but also presence of an on-site ICU. However, further sensitivity analyses including only infants that met at least three out of four preset criteria for escalation of care stratified by presence of an on-site ICU consistently favoured high-flow oxygen over standard therapy. In addition, Franklin *et al*. [6] did not mention whether there were any children who should have been escalated according to these criteria, but were not. Those children were not included in the sensitivity analysis and it is difficult to predict how this would have affected the results.

The comparatively higher cost of high-flow oxygen was not discussed by Franklin *et al*. [6]. Also, most of the infants in the standard-therapy

group did not require escalation of care, which indicates that most would not benefit from initial high-flow oxygen treatment. Additionally, no differences between the two groups were observed in any of the secondary outcomes, such as transfer to the ICU or intubation. In spite of the fact that escalation of care was experienced by fewer infants in the high-flow group, overall the cost–benefit balance would favour initiating treatment with traditional nasal cannula.

Most of the previous evidence for high-flow oxygen treatment of bronchiolitis comes from observational studies [7]. Among the few randomised controlled trials comparing high-flow oxygen to standard, low-flow oxygen therapy in infants with bronchiolitis [8, 9], this study by Franklin *et al*. [6] is the largest, and the most important.

Implications for practice

The escalation of care results of Franklin *et al*. [6] favour high-flow oxygen over standard nasal cannula. In the absence of other large randomised controlled trials, however, aspects of this study's design and interpretation of its results, and the higher costs of high-flow therapy need to be considered before implementing high-flow therapy as initial therapy; previous commentators have also raised these points [10–13]. Further research is needed to establish the best moment to start high-flow oxygen therapy in hypoxaemic infants with bronchiolitis. In the meantime, clinicians should assess the individual situation of each patient before deciding to initiate high-flow oxygen therapy.

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Conflict of interest

None declared.

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10.5 Co-author publication: Diagnosis of asthma in children: the contribution of a detailed history and test results

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Own contribution: Help with conceptualization of study, help with data interpretation, revise manuscript, proof reading before publishing.

Diagnosis of asthma in children: the contribution of a detailed history and test results

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Diagnosing asthma in children is most accurately done by using information on triggers and severity of wheeze and by F_{eNO} measurement, methacholine and exercise challenge tests. http://bit.ly/2kDWaRr

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ABSTRACT

Introduction: There are few data on the usefulness of different tests to diagnose asthma in children.

Aim: We assessed the contribution of a detailed history and a variety of diagnostic tests for diagnosing asthma in children.

Methods: We studied children aged 6–16 years referred consecutively for evaluation of suspected asthma to two pulmonary outpatient clinics. Symptoms were assessed by parental questionnaire. The clinical evaluation included skin-prick tests, measurement of exhaled nitric oxide fraction (F_{eNO}), spirometry, bronchodilator reversibility and bronchial provocation tests (BPT) by exercise, methacholine and mannitol. Asthma was diagnosed by the physicians at the end of the visit. We assessed diagnostic accuracy of symptoms and tests by calculating sensitivity, specificity, positive and negative predictive values and area under the curve (AUC).

Results: Of the 111 participants, 80 (72%) were diagnosed with asthma. The combined sensitivity and specificity was highest for reported frequent wheeze (more than three attacks per year) (sensitivity 0.44, specificity 0.90), awakening due to wheeze (0.41, 0.90) and wheeze triggered by pollen (0.46, 0.83) or by pets (0.29, 0.99). Of the diagnostic tests, the AUC was highest for F_{eNO} measurement (0.80) and BPT by methacholine (0.81) or exercise (0.74), and lowest for forced expiratory volume in 1 s (FEV_1) (0.62) and FEV_1/forced vital capacity ratio (0.66), assessed by spirometry.

Conclusion: This study suggests that specific questions about triggers and severity of wheeze, measurement of F_{eNO} and BPT by methacholine or exercise contribute more to the diagnosis of asthma in school-aged children than spirometry, bronchodilator reversibility and skin-prick tests.

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Introduction

Diagnosing asthma in children is not straightforward, because we lack a stand-alone diagnostic test. Symptoms (cough, wheeze, breathlessness) are not specific for asthma and interpretation of commonly used diagnostic tests is complicated by the temporal variability and phenotypic heterogeneity of asthma. Thus, diagnostic guidelines suggest diagnosing asthma based on a characteristic pattern of respiratory symptoms, clinical examination, demonstration of reversible airway obstruction assessed by spirometry and airway inflammation measured by exhaled nitric oxide fraction (F_{eNO}) [1–4]. Allergy tests and measurement of bronchial hyperresponsiveness by direct and indirect challenge tests are used as further aids for diagnosis.

However, the diagnostic algorithm proposed by recent guidelines has been questioned for children and there are surprisingly few data available to assess the usefulness of the different tests in the diagnosis of asthma in school-aged children [5]. Systematic literature reviews done for recent guidelines and for the ongoing taskforce of the European Respiratory Society identified only a handful of publications assessing the accuracy of the different tests for children with suspected asthma [2, 3]. Most publications identified by the searches had a case–control design, comparing children with asthma to healthy controls instead of consecutive referrals of children suspected of having asthma. Available studies had included only few diagnostic tests and no detailed history, and asthma diagnosis used as reference standard was often poorly defined or too narrow, for instance including only allergic asthma. Additionally, papers used different cut-offs for positive tests (*e.g.* for F_{eNO} or forced expiratory volume in 1 s (FEV_1)), and it remains unclear which cut-offs are best for children [1–4]. In this study, we assessed the diagnostic accuracy of reported respiratory symptoms and different objective tests to diagnose asthma in consecutive referrals of school-aged children presenting symptoms suggestive of asthma.

Methods

Study population and study design

For this study, we re-analysed data from a clinical study performed in 2007–2008 in Switzerland. It included consecutive first-time referrals to the respiratory outpatient clinics of two paediatric hospitals (St Gallen and Basel) of 6–16-year-old children for evaluation of a possible asthma diagnosis with a history of wheezing, dyspnoea or cough. Children were excluded from the study if they had a known chronic respiratory disease such as cystic fibrosis, or a respiratory tract infection during the 4 weeks prior to the visit. The aim of the initial study had been to compare the results of mannitol challenge tests to exercise challenge tests [6].

Study procedures

All children referred for the first time by general practitioners or primary care paediatricians for evaluation of possible asthma were invited to participate in the study, which included two visits to the hospital within a week (figure 1). At the first visit, all children underwent clinical evaluation, skin-prick testing (unless printed results of a skin-prick test done during the past 2 years were available), measurement of F_{eNO}, spirometry, exercise bronchial provocation tests (BPT), methacholine BPT and bronchodilator reversibility test, in that order. Children who reacted to the exercise challenge and received salbutamol returned for an extra visit within the following few days to perform the methacholine challenge test. Within a week all children repeated the F_{eNO} measurement and performed a mannitol BPT. Between visits, the family completed a questionnaire. Ethical approval was obtained from the local ethics committee and all parents gave informed consent at baseline (EKSG 07/001).

Clinical asthma diagnosis (reference standard)

The study physicians, experienced paediatric pulmonologists, completed a physician's report form that included the clinical diagnosis (definite asthma, probable asthma or other disease), at two time points. At the first visit, physicians considered only medical history, clinical examination, allergy tests, F_{eNO} measurement and spirometry. At the second visit, the same physician reported the clinical diagnosis (as definite asthma, probable asthma or other disease) in the second physicians' report form, taking into account all the information available, *i.e.* medical history, clinical examination, allergy tests, F_{eNO} measurement, spirometry and results of the BPT and bronchodilator reversibility test. For our main analysis, we defined asthma (reference standard) as an affirmative answer to either definite or probable asthma in the second physician's report form. In a sensitivity analysis, we used the first physicians' report form (based on all the information except the BPTs) to define asthma (reference standard).

Assessment of respiratory symptoms and diagnostic testing

The parental questionnaire included the International Study of Asthma and Allergies in Childhood (ISAAC) key questions for lower respiratory symptoms and more detailed questions on wheeze and cough

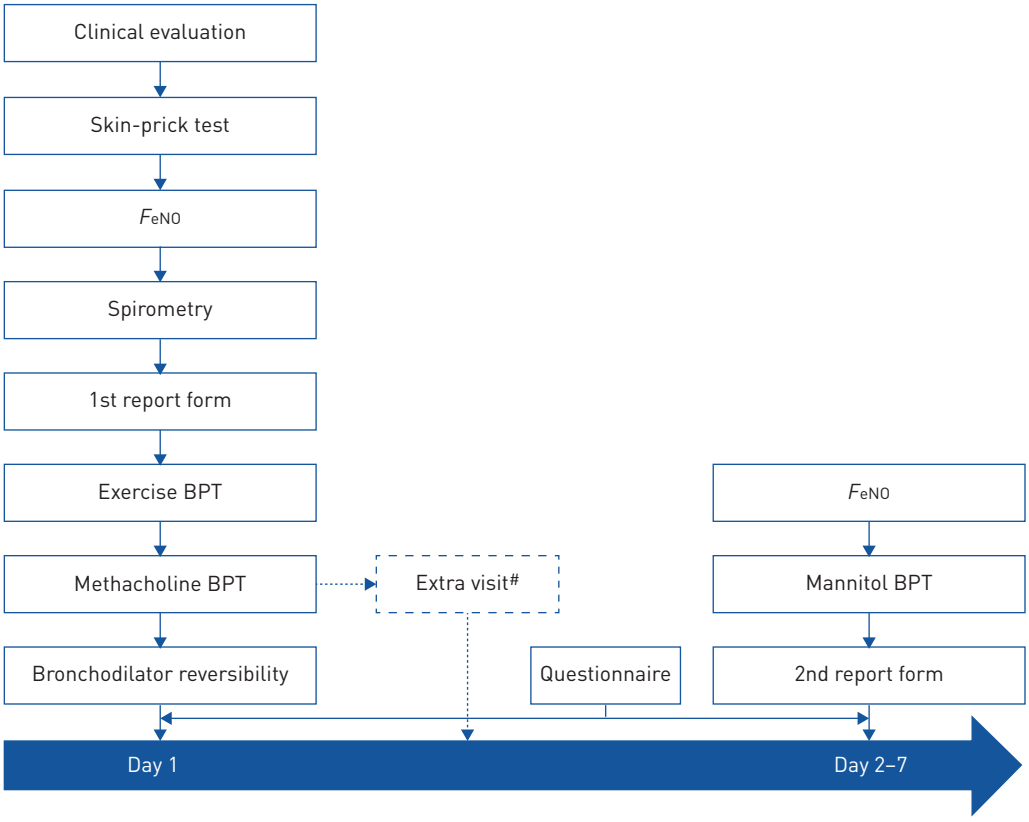

FIGURE 1 Study procedures. The report form is a standardised form for physicians to note down the clinical diagnosis. BPT: bronchial provocation test; F_{eNO}: fractional exhaled nitric oxide. #: children who received salbutamol after the exercise BPT conducted the methacholine BPT at an additional visit.

derived from the questionnaires used in the Leicester respiratory cohort studies (supplementary material) [7, 8]. All diagnostic tests were performed according to published guidelines [9–13]. Short-acting β_2-agonists were withheld for 8 h, inhaled corticosteroids, leukotriene antagonists and long-acting β_2-agonists for 24 h and antihistamines and sodium cromoglicate for >72 h.

Skin-prick test

We performed skin-prick tests using birch, grass, mugwort, alternaria, cat, house dust mites (*Dermatophagoides pteronyssinus*), histamine and saline. The skin-prick test was considered positive if the allergen wheal size was ⩾3 mm, the positive control (histamine) wheal size was ⩾3 mm and the negative control (saline) wheal size was <3 mm. These allergens cover 95% of allergies to inhaled allergens in Switzerland [14].

F_{eNO}

F_{eNO} was measured in doublets before spirometry, using the portable multi-gas analyser (NIOX MINO, Aerocrine, Sollentuna, Sweden), in accordance with published guidelines [10] and previous studies using this device [15, 16]. The portable analyser ensures a constant expiratory flow of 50±5 mL·s^{-1}, has an accuracy of ±10% with a minimum ±5 ppb and the quality was controlled by the lung function technician according to the manufacturer's guidelines.

Spirometry

Spirometry was performed using American Thoracic Society (ATS) criteria for paediatric lung function testing and a Jaeger Masterscope (Erich Jaeger, Würzburg, Germany), using JLAB software (version 4.34). Spirometry was performed in triplicate by experienced lung function technicians, who performed quality control during the measurement and recorded the best measurement. The flow–volume curve was then checked by the responsible paediatric pulmonologist. Results are expressed as proportion (FEV_1/forced vital capacity (FVC)) and as z-scores based on Global Lung Initiative 2012 reference standards [17].

Bronchial provocation tests

For all BPTs, baseline FEV_1 was measured in triplicate using ATS criteria for paediatric lung function testing [9] and the best measurement was recorded. We reported the results of the exercise BPT as the maximum fall of FEV_1 compared to baseline, the methacholine BPT as provocation dose causing a 20% decrease of FEV_1 from baseline (PD_{20}) and the mannitol BPT as provocation dose causing a 15% decrease of FEV_1 from baseline (PD_{15}). After the methacholine BPT, all children were given four puffs of salbutamol 100 µg to test for bronchodilator reversibility. In addition, children received salbutamol if FEV_1 had not returned to within 5% of baseline 15 min after the exercise or mannitol BPT, or in cases of dyspnoea. More details on the BPTs have been published before and can be found in the supplementary material [6].

Statistical analysis

For the reported respiratory symptoms and the different tests, we calculated sensitivity, specificity, positive predictive value and negative predictive value, Youden's index (sensitivity+specificity−1), area under the curve (AUC) and their 95% confidence intervals to diagnose asthma, using the final (post-BPT) physicians' diagnosis as reference standard. We did a sensitivity analysis using the first (pre-BPT) physicians' diagnosis. We displayed the cut-off values with the highest Youden's index in our study and those used in the literature. We used STATA software (version 15; College Station, TX, USA) for statistical analysis.

Results

Characteristics of the study population

Of the 124 children invited, 111 (90%) were recruited, 84 from St Gallen and 27 from Basel. The median (range) age was 12 (6–16) years and 62% were male. Most children were referred with wheeze and cough (47%) or wheeze without cough (23%). Inhaled medication had been used by 64% prior to referral, including 19% who had used inhaled corticosteroids (table 1). Of the 111 participants, 80 (72%) were diagnosed with asthma after all BPTs were done compared to 94 (85%) before the BPTs. The remaining children were diagnosed with cough unrelated to asthma (8% before BPTs and 13% after BPTs) and with inducible laryngeal obstruction and dysfunctional breathing (6% before BPTs and 7% after BPTs) (supplementary table S1). None of the children were diagnosed with a severe lung disease such as cystic fibrosis [18].

TABLE 1 Characteristics of the study participants

Age years	11 (6–16)
Male	69 (62)
Respiratory symptoms in the past 12 months	
Any wheeze	80 (72)
>3 attacks of wheeze	38 (34)
Wheeze with colds	43 (39)
Wheeze apart from colds	67 (60)
Exercise-induced wheeze	70 (63)
Wheeze triggered by pollen	36 (32)
Wheeze triggered by house dust	21 (19)
Wheeze triggered by pets	20 (18)
Awakening due to wheeze	36 (32)
Cough lasting >4 weeks	21 (19)
Night cough	48 (43)
Cough more than others	37 (33)
Dyspnoea	25 (23)
Hay fever[#]	49 (44)
Eczema[#]	26 (23)
Inhaled medication	
Any	71 (64)
Short-acting β_2-agonist, alone	49 (44)
ICS + short-acting β_2-agonist	6 (5)
ICS + long-acting β_2-agonist	16 (14)

Data are presented as median (range) or n (%). n=111. ICS: inhaled corticosteroids. [#]: ever in the past.

Diagnostic accuracy of respiratory symptoms to diagnose asthma

Reported wheeze in the past 12 months had the highest sensitivity (80%) for physician-diagnosed asthma (table 2). Specificity was highest for frequent wheeze (more than three attacks per year) (90%), awakening due to wheeze (90%) and wheeze triggered by pollen (83%), house dust (93%) or pets (99%). Combined sensitivity and specificity was highest for frequent wheeze in the past 12 months (Youden's index 0.34), awakening due to wheeze (0.31) and wheeze triggered by pollen (0.29) or pets (0.28) (table 2).

Diagnostic accuracy of tests to diagnose asthma

All 111 children completed skin-prick testing, F_{eNO}, spirometry and BPT by mannitol. BPT by exercise could not be completed in 12 children because of exhaustion (n=7), inspiratory stridor (induced laryngeal obstruction) (n=2), no cooperation (n=2) or technical difficulties (n=1) [6, 19]. Seven patients could not complete BPT by methacholine due to exhaustion and 36 children performed the test during an extra visit a few days later. In four patients the skin-prick test result was not considered valid because the histamine control was not positive. Test results in patients with and without asthma diagnosis are displayed in supplementary table S2.

The cut-off values with the best diagnostic accuracy were <80% for FEV_1/FVC, ⩽−0.8 z-score for FEV_1, ⩾10% increase of FEV_1 for bronchodilator reversibility test, ⩾8% decrease of FEV_1 for BPT by exercise, PD_{20} <0.7 mg for BPT by methacholine, PD_{15} <635 mg for BPT by mannitol, ⩾2 for the number of positive skin-prick tests, ⩾8 mm for the cumulative wheal size of skin-prick tests and ⩾21 ppb for F_{eNO} (table 3).

Accuracy overall was best for F_{eNO}, BPT by methacholine and BPT by exercise (AUC 0.80, 0.81 and 0.74, respectively). Accuracy was lower for BPT by mannitol and skin-prick test (AUC ~0.70), and lowest for spirometry (AUC 0.62 and 0.66 for FEV_1 and FEV_1/FVC ratio, respectively) (figure 2).

Sensitivity analysis

In the sensitivity analysis with asthma diagnosis based on the pre-BPT report form, frequent wheeze and wheeze triggered by pollen or by pets in the past 12 months had the highest Youden's index, which was in line with the main analysis. In addition, night cough and hay fever had a high Youden's index for the asthma diagnosis pre-BPT (supplementary table S3), but not for the asthma diagnosis post-BPTs (table 2).

For the diagnostic tests, the Youden's index was highest at the same cut-offs for most tests (supplementary table S4 and supplementary figure S1). Cut-offs were higher for F_{eNO} (25 *versus* 21) and lower for BPT by exercise (6 *versus* 8), FEV_1 (−0.6 *versus* −0.8) and bronchodilator reversibility (2 *versus* 10).

The accuracy was higher pre-BPT than post-BPT for spirometry (AUC 0.71 for FEV_1/FVC and 0.65 for FEV_1 *versus* 0.66 and 0.62, respectively) and bronchodilator reversibility (AUC 0.72 *versus* 0.58) and lower for the BPTs (AUC 0.70 for exercise, 0.68 for methacholine and 0.60 for mannitol *versus* 0.74, 0.81 and 0.68, respectively). Accuracy was best for F_{eNO} measurement, bronchodilator reversibility, FEV_1/FVC ratio and BPT by methacholine and by exercise (AUC 0.78, 0.72, 0.71, 0.70 and 0.70, respectively).

TABLE 2 Diagnostic accuracy of respiratory symptoms in the past 12 months to diagnose asthma

	A^+S^+	A^-S^+	A^+S^-	A^-S^-	Sensitivity	Specificity	PPV	NPV	Youden's index[#]
Any wheeze	64	16	16	15	80 (70–88)	48 (30–67)	80 (70–88)	48 (30–67)	0.28
>3 attacks of wheeze	35	3	45	28	44 (33–55)	90 (74–98)	92 (79–98)	38 (27–50)	0.34
Wheeze with colds	32	11	48	20	40 (29–52)	65 (45–81)	74 (59–86)	29 (19–42)	0.05
Wheeze apart from colds	54	13	26	18	68 (56–78)	58 (39–75)	81 (69–89)	41 (26–57)	0.26
Exercise-induced wheeze	54	16	26	15	68 (56–78)	48 (30–67)	77 (66–86)	37 (22–53)	0.16
Wheeze triggered by:									
Pollen	31	5	37	24	46 (33–58)	83 (64–94)	86 (71–95)	39 (27–53)	0.29
House dust	19	2	46	26	29 (19–42)	93 (76–99)	90 (70–99)	36 (25–48)	0.22
Pets	20	0	50	17	29 (18–41)	99 (80–99)	99 (83–99)	25 (16–37)	0.28
Awakening due to wheeze	33	3	47	28	41 (30–53)	90 (74–98)	86 (71–95)	37 (26–49)	0.31
Cough lasting >4 weeks	11	10	68	21	14 (7–24)	68 (49–83)	52 (30–74)	24 (15–34)	−0.18
Night cough	38	10	42	20	48 (36–59)	67 (47–83)	79 (65–90)	32 (21–45)	0.15
Cough more than others	28	9	52	21	35 (25–46)	70 (51–85)	76 (59–88)	29 (19–41)	0.05
Dyspnoea	21	4	58	26	27 (17–38)	87 (69–96)	84 (64–95)	31 (21–42)	0.14
Hay fever[¶]	40	9	38	22	51 (40–63)	71 (52–86)	82 (68–91)	37 (25–50)	0.22
Eczema[¶]	21	5	58	25	27 (17–38)	83 (65–94)	81 (61–93)	30 (21–41)	0.10

Data are presented as n or % (95% CI), unless otherwise stated. n=111. A^+S^+: children with asthma diagnosis and reported symptom; A^-S^+: children without asthma diagnosis but with symptom; A^+S^-: children with asthma diagnosis but without symptom; A^-S^-: children without asthma and without symptom; PPV: positive predictive value; NPV: negative predictive value. [#]: sensitivity+specificity−1; [¶]: ever in the past.

TABLE 3 Diagnostic accuracy of clinical tests to diagnose asthma

	A^+T^+	A^-T^+	A^+T^-	A^-T^-	Sensitivity	Specificity	PPV	NPV	Youden's index[#]	AUC
Clinical tests										
Skin-prick test[¶]										0.70
⩾1 positive test	69	18	8	12	90 (81–95)	40 (23–59)	79 (69–87)	60 (32–81)	0.30	
⩾2 positive tests[+]	61	14	16	16	79 (68–88)	53 (34–72)	81 (71–89)	50 (32–68)	0.32	
Skin-prick test[§]										0.72
⩾4 mm	63	16	12	14	84 (74–91)	47 (28–66)	80 (69–88)	54 (33–73)	0.31	
⩾8 mm[+]	46	7	29	23	61 (49–72)	77 (58–90)	87 (75–95)	44 (30–59)	0.38	
F_{eNO}										0.80
⩾21 ppb[+]	47	4	33	27	59 (47–70)	87 (70–96)	92 (81–98)	45 (32–58)	0.46	
⩾22 ppb	44	4	36	27	55 (43–66)	87 (70–96)	92 (80–98)	43 (30–56)	0.42	
⩾25 ppb	40	2	40	29	50 (39–61)	94 (79–99)	95 (84–99)	42 (30–55)	0.44	
⩾35 ppb	31	2	49	29	39 (28–50)	94 (79–99)	94 (80–99)	37 (26–49)	0.33	
Spirometry										
FEV_1/FVC										0.66
<70%	6	0	74	30	8 (3–16)	99 (88–99)	99 (54–99)	29 (20–39)	0.08	
<80%[+]	37	2	43	28	46 (35–58)	93 (78–99)	95 (83–99)	39 (28–52)	0.40	
<90%	66	22	14	8	83 (72–90)	27 (12–46)	75 (65–84)	36 (17–59)	0.09	
FEV_1										0.62
⩽−0.8[+]	35	7	45	24	44 (33–56)	77 (59–90)	83 (69–93)	35 (24–47)	0.21	
⩽−1.0	28	5	52	26	35 (25–47)	84 (66–95)	85 (68–95)	33 (23–45)	0.19	
Bronchodilator reversibility										0.58
⩾10% increase FEV_1[+]	20	3	54	26	27 (17–39)	90 (73–98)	87 (66–97)	33 (22–44)	0.17	
⩾12% increase FEV_1	16	3	58	26	22 (13–33)	90 (73–98)	84 (60–97)	31 (21–42)	0.11	
BPT										
Exercise										0.74
⩾8% decrease FEV_1[+]	47	5	28	19	63 (51–74)	79 (58–93)	90 (79–97)	40 (26–56)	0.42	
⩾10% decrease FEV_1	39	4	36	20	52 (40–64)	83 (63–95)	91 (78–97)	36 (23–50)	0.35	
⩾12% decrease FEV_1	33	2	42	22	44 (33–56)	92 (73–99)	94 (81–99)	34 (23–47)	0.36	
Methacholine										0.81
PD_{20} <0.7 mg[+]	62	8	13	21	83 (72–90)	72 (53–87)	89 (79–95)	62 (44–78)	0.55	
PD_{20} <1 mg	64	9	11	20	85 (75–92)	69 (49–85)	88 (78–94)	65 (45–81)	0.54	
Mannitol										0.68
PD_{15} <635 mg[+]	31	1	49	30	39 (28–50)	97 (83–99)	97 (84–99)	38 (27–50)	0.36	

Data are presented as n or % (95% CI), unless otherwise stated. n=111. Cut-offs chosen based on proposed cut-offs from previous publications. A^+T^+: children with asthma diagnosis and positive test result; A^-T^+: children without asthma diagnosis but positive test result; A^+T^-: children with asthma diagnosis but negative test result; A^-T^-: children without asthma and negative test result; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve; F_{eNO}: exhaled nitric oxide fraction; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BPT: bronchial provocation test; PD_{20}: provocation dose causing a 20% decrease of FEV_1 from baseline; PD_{15}: provocation dose causing a 15% decrease of FEV_1 from baseline. [#]: sensitivity+specificity−1; [¶]: number of allergens for which the skin-prick test is positive: wheal size ⩾3 mm; [+]: cut-off with maximum combined sensitivity and specificity (highest Youden's index); [§]: cumulative wheal size.

Discussion

This is the first study to systematically assess the diagnostic accuracy of reported symptoms and a range of tests in asthma diagnosis in children compared to a defined reference standard (doctor-diagnosed asthma based on all available measurements and information). The main analysis and sensitivity analysis showed broadly comparable results, suggesting that a history of frequent wheeze, awakening due to wheeze and wheeze triggered by pollen or pets, F_{eNO} measurement, BPT by methacholine and BPT by exercise have the best ability to distinguish asthma from no asthma. FEV_1, FEV_1/FVC ratio and bronchodilator reversibility had low accuracy.

Only three other studies have assessed the accuracy of symptoms to diagnose asthma in school-aged children consecutively referred to paediatric hospitals [20–22]. They all found that reported wheeze was sensitive (range 0.75–0.86), but not specific (0.64–0.73) and that frequent wheeze and awakening due to dyspnoea were specific (0.84–0.90), but not sensitive (0.33–0.54), which is in line with our findings. Symptom definitions differed between studies, especially those for cough, which results in a wide range of sensitivities and specificities that cannot be compared [20–22]. Five other studies assessed the accuracy of diagnostic tests in school-aged children. Woo *et al.* [23] found that positive skin-prick tests were sensitive, but not specific (sensitivity and specificity 0.68 and 0.32, respectively) and that F_{eNO} had the best cut-off at 22 ppb (0.57 and 0.87, respectively), which was comparable with our study (21 ppb, 0.59 and 0.87,

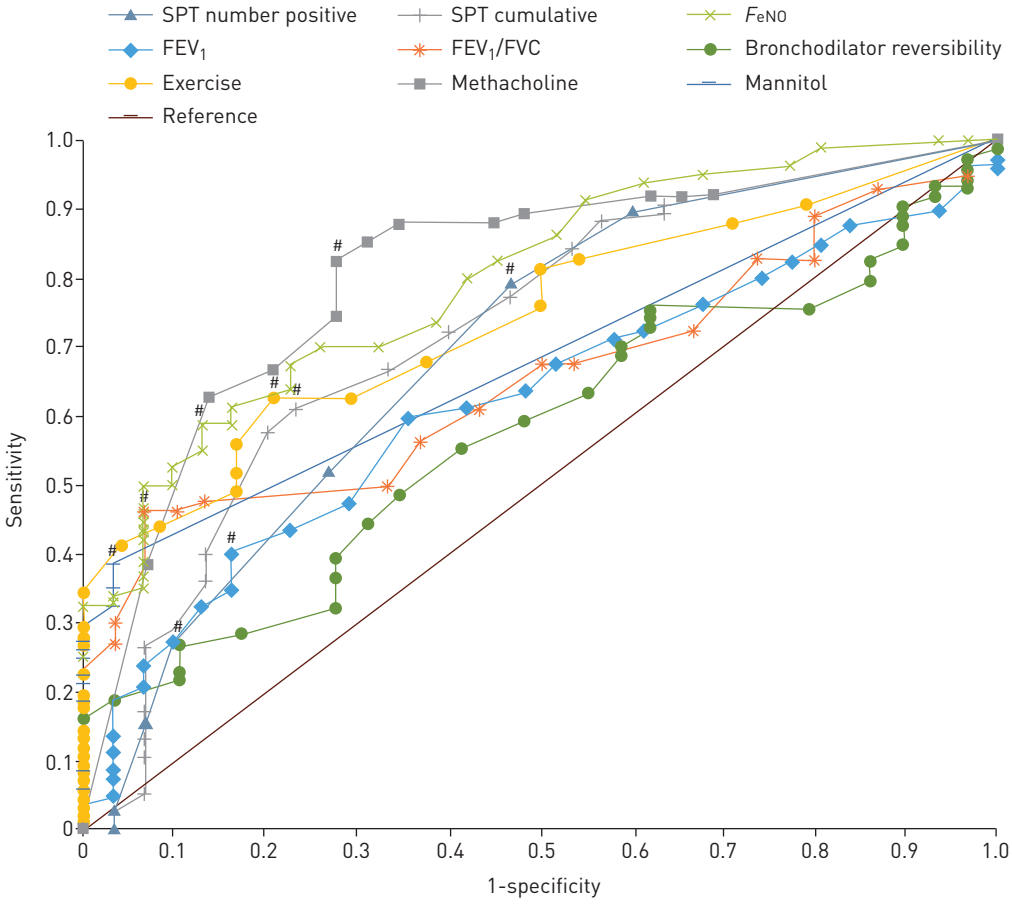

FIGURE 2 Receiver operating characteristic (ROC) curve of clinical tests to diagnose asthma. Test (unit): skin-prick test (SPT) number positive (decrease of 1 positive SPT); SPT cumulative wheal size (decrease of 1 mm cumulative wheal size); exhaled nitric oxide fraction (F_{eNO}) (decrease of 1 ppb); forced expiratory volume in 1 s (FEV_1) (increase of 0.1 z-score); FEV_1/forced vital capacity (FVC) (increase of 1%); bronchodilator reversibility (increase of 1% in FEV_1); exercise (decrease of 1% in FEV_1); methacholine (increase of 0.1 mg methacholine); mannitol (increase of 5 mg mannitol). #: cut-off with maximum combined sensitivity and specificity.

respectively). Grzelewski *et al.* [24] found that a FEV_1/FVC ratio of <80% was specific (0.91), but not sensitive (0.12) for asthma, which is in line with our findings (<79%; 0.90 and 0.46, respectively). For the bronchodilator reversibility test, Galant *et al.* [25] and Dundas *et al.* [26] found a 9% increase in FEV_1 to be the best cut-off to diagnose asthma, which is in line with our findings (10%); however, they compared children with asthma to healthy children. For BPT by exercise, Avital *et al.* [27] found an 8% decrease in FEV_1 to be the best cut-off for asthma diagnosis, which is the same as we found. For BPT by methacholine, Zaczeniuk *et al.* [28] reported a best cut-off of <0.7 mg, which was in line with our study. Anderson *et al.* [29] found a sensitivity of 0.63 and specificity of 0.81 for the widely used best cut-off of <635 mg for BPT by mannitol, while we found a lower sensitivity and higher specificity (0.43 and 0.93, respectively).

The recent National Institute for Health and Care Excellence (NICE) asthma diagnostic algorithm has been questioned in children. Murray *et al.* [5] tested the algorithm in the Manchester Asthma and Allergy Study, a population-based cohort of 1184 children aged 13–16 years, of whom 89 were symptomatic, but not regularly inhaling corticosteroids. However, the Manchester study relied on parent-reported data to define asthma (reported wheeze and asthma treatment in the past 12 months plus a doctor diagnosis of asthma ever in life) and compared children with asthma to healthy children, leaving out from the analysis all those with possible asthma. In clinical practice we want to distinguish children with asthma from children with respiratory symptoms due to other causes, not from healthy children. If we had applied the NICE algorithm to our clinical population, only four out of the 111 children would have been diagnosed with asthma at the initial visit (FEV_1/FVC ratio <70% and bronchodilator reversibility of ⩾12%). 106 would have needed 2 weeks peak expiratory flow monitoring followed by a second visit. In addition, we

found that less stringent cut-off values had higher sensitivity and specificity than those recommended by the NICE algorithm (FEV_1/FVC ratio <80% *versus* <70%, bronchodilator reversibility ⩾10% *versus* ⩾12% and F_{eNO} ⩾26 ppb *versus* ⩾35 ppb, respectively). This highlights the need to base diagnostic algorithms for children on clinical studies done in children, rather than in adults.

A main strength of our study is that it represents a real-life situation in everyday paediatric practice. With the clinical design, it reflects the typical mix of patients in a paediatric outpatient clinic. All children were first-time referrals for evaluation of possible asthma, which is the patient group the diagnostic tests are intended for. Therefore, the study population is representative of daily clinical practice, in contrast to many published studies that selectively include well-defined moderate-to-severe asthmatics comparing them to healthy controls and excluding patients with unclear degrees of airway reactivity. In addition, our patients had an extensive array of examinations for lung function, BPT and allergy, which allowed us to assess the accuracy of different symptoms and diagnostic tests simultaneously.

An important limitation of this study was that the reference standard for asthma diagnosis (the final diagnosis by the physician) took into account the results of the patient history and diagnostic tests for which the accuracy was assessed. However, as there is no single objective test to diagnose asthma and be used as a comparator, the clinician's judgement, taking into account the full history, examination and test results, is the best we can do. The sensitivity analysis using the physicians' diagnosis before BPTs were performed, showed comparable results. However, the small differences highlight the dependence of the physician's diagnosis on the array of tests performed. The reference diagnosis of asthma was made by experienced paediatric pulmonologists (three in Basel and two in St Gallen), trained in Switzerland, who met several times prior to and during the study to standardise their procedures and minimise centre-specific effects. In this study we restricted analysis to basic clinical tests. The advantage of this approach is that most of these tests are available in clinical routine. However, future studies should also evaluate the diagnostic accuracy of newer techniques such as component-resolved IgE diagnostic, multiple-breath or single-breath washout techniques.

Our findings, which need to be replicated in other populations of patients, will help to propose a more evidence-based paediatric diagnostic algorithm, which incorporates both information on symptoms and objective measures. This might be helpful in reducing the need for trials of asthma treatment, which can be costly, time consuming and can lead to misdiagnosis and overtreatment. Our study is therefore an important contribution to the small body of evidence about the value of different tests for the diagnosis of paediatric asthma on which guidelines should be based. Mild paediatric asthma is a disease with highly variable activity and paroxysmal clinical manifestation. It seems unlikely that any test performed at a specific time point will be accurate enough to either prove or exclude reactive airway disease. Future studies should ideally be larger, to allow analysing the value of combination of several tests, and focus on children newly referred for evaluation of possible asthma, and be referenced to a clearly defined and robust reference diagnosis.

Our results suggest that, until more evidence is available, diagnosis of asthma in school-aged children should rely primarily on reported triggers and severity of wheeze and results of F_{eNO}, and, if available, methacholine and exercise challenge testing which were most accurate in our study.

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Author contributions: C.E. Kuehni and J. Barben conceptualised and designed the study. D. Trachsel and J. Barben supervised data collection. C.C.M. de Jong analysed the data and drafted the manuscript. E.S.L. Pedersen and M. Goutaki supported the statistical analysis and gave input for interpretation of the data. All authors critically revised the manuscript and approved the final manuscript as submitted.

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10.6 First-author publication: Addressing selection bias in diagnostic accuracy studies

Pedersen ESL, de Jong CCM.

Letter to the editor

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Own contribution: Conceptualize study, draft manuscript, submit manuscript to journal, implement reviewer comments, proof read.

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Addressing selection bias in diagnostic accuracy studies

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Exercise-challenge testing is the reference standard method to diagnose exercise-induced bronchoconstriction (EIB). This method requires advanced technical equipment, is time consuming and involves active cooperation. For these reasons, researchers try to use other tests to diagnose EIB. Fractional exhaled nitric oxide (FeNO) has been proposed as an alternative method of diagnosing EIB, but it is not clear how accurate this test is.

We read with great interest the study by Kim *et al.*,[1] which investigated the diagnostic accuracy of FeNO in predicting EIB in children with asthma. The study was performed using clinical routine data from asthmatic children aged 6–16 years. A total of 60 of 242 children (25%) had both FeNO and exercise-challenge tests. It was found that FeNO was positively associated with a fall in forced expired volume in the first second (FEV1) after exercise, and that FeNO had the ability to detect a fall in FEV1 $\geq$ 10% with an area under the curve (AUC) of 0.77. The optimal FeNO cut-off was 20 p.p.b. with a sensitivity of 82% and specificity of 61%. The authors concluded that FeNO may be a clinically useful diagnostic tool for diagnosing EIB in children.

The study was based on retrospectively collected routine care data of which only a fraction of children seen in the outpatient clinics was included: namely, those who had both FeNO and exercise-challenge test. Usually clinical testing such as FeNO and exercise-challenge testing are performed by indication, for example due to asthma severity or symptom patterns. Therefore, the subjects (children who had both tests) were probably not equal to the target population (children with asthma). This kind of selection bias, also called referral bias, has been associated with a falsely raised sensitivity of the test in question.[2–4] We believe that this selection bias is important to account for when judging whether FeNO can be used to diagnose EIB.

Evidence from other studies shows that FeNO is linearly associated with a fall in FEV1 after exercise, but the strength of the association and whether it is possible to set a cut-off for diagnosing EIB in children is not clear. A study including an unselected sample of 121 children aged 6–15 years with mild–moderate asthma found that the optimal FeNO cut-off point depended on whether the children were currently on inhaled corticosteroids (cut-off, 12 p.p.b.) or not (cut-off, 21 p.p.b.).[5] Another study in an unselected sample of 224 children at high risk of asthma found FeNO to be associated with a fall in FEV1 but that no cut-off point could be found to predict EIB.[6] This shows that the characteristics of the study sample influence the ability of FeNO to accurately diagnose EIB.

We commend Kim *et al.* for their valuable contribution to the evidence on the predictive properties of FeNO to predict EIB in children. It seems that FeNO is related to EIB and may be used for diagnosing EIB, but more studies in unselected asthmatic children are needed in order to judge the generalizability of the existing findings and to identify the optimal FeNO cut-off for predicting EIB in children. We believe it is important to consider the effect of bias in diagnostic accuracy studies. Tools such as QUADAS-2[7] could be used as a checklist before conducting a study, to ascertain the risk of bias and thereby increase the quality of future studies.

Disclosure

The authors declare no conflict of interest.

Author contributions

The manuscript was written and revised by both authors.

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10.7 Co-author publication: Diagnosis of asthma in children – findings from the Swiss Paediatric Airway Cohort

De Jong CCM, **Pedersen ESL**, Mozun R, Müller-Suter D, Jochmann A, Singer F, Casaulta C, Regamey N, Barben J, Moeller A, Ardura-Garcia C, Kuehni CE.

Original article

Own contribution: Help collect and enter data, help with conceptualization of study, help with data interpretation, revise manuscript.

Diagnosis of asthma in children – findings from the Swiss Paediatric Airway Cohort

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Take Home Message (137/256 characters): Asthma diagnosis seems not straightforward even for experienced pulmonologist, which highlights the need for new evidence-based guidance.

Conflict of interest: None

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Author Contributions: C. Kuehni and C. de Jong conceptualised and designed the study. D. Müller-Suter, A. Jochmann, F. Singer, C. Casaulta, N. Regamey, and A. Moeller supervised data collection. C. de Jong analysed the data and drafted the manuscript. E. Pedersen and C. Ardura supported the statistical analysis and gave input for interpretation of the data. All authors critically revised the manuscript and approved the final manuscript as submitted.

Keywords: asthma, wheeze, diagnostic testing, cohort, children, Switzerland

Word count: 2995/3000

Abstract (245/250)

Introduction: Diagnosing asthma in children remains a challenge, because respiratory symptoms are not specific and vary over time.

Aim: In a real-life observational study, we assessed the diagnostic accuracy of respiratory symptoms, objective tests and two proposed paediatric diagnostic algorithms by GINA and NICE to diagnose asthma in school-aged children referred for suspected asthma to respiratory outpatient clinics.

Methods: We studied children aged 5-17 years referred consecutively for evaluation of suspected asthma to pulmonary outpatient clinics. Symptoms were assessed by parental questionnaire. The clinical evaluation included specific IgE measurement or skin prick tests, measurement of fractional exhaled nitric oxide (FeNO), spirometry, body plethysmography and bronchodilator reversibility. Asthma was diagnosed by physicians based on the GINA guideline. We assessed diagnostic accuracy of symptoms, tests and diagnostic algorithms by calculating sensitivity, specificity, positive and negative predictive values, and area under the curve (AUC).

Results: Of the 514 participants, 357(70%) were diagnosed with asthma. The combined sensitivity and specificity (sensitivity/specificity) was highest for any wheeze (0.75/0.65), dyspnoea (0.56/0.76), and wheeze triggered by colds (0.58/0.78) or by exercise (0.55/0.74). Of the diagnostic tests, the AUC was highest for specific total resistance (sRtot) (0.73) and lowest for the residual volume (RV) total lung capacity (TLC) ratio (0.56). The NICE algorithm had a sensitivity of 0.69 and specificity of 0.67, whereas the GINA algorithm had a sensitivity of 0.42 and specificity of 0.90.

Conclusion: Asthma diagnosis seems not straightforward even for experienced pulmonologist, which highlights the need for new evidence-based guidance.

Introduction

Diagnosing asthma in children remains a challenge, because respiratory symptoms such as wheeze and cough are not specific and vary over time, and a stand-alone diagnostic test is lacking. Clinically, physicians diagnose asthma based on a combination of symptoms, physical examination and a diagnostic tests [1-3]. Of these, spirometry and body plethysmography in combination with bronchodilator reversibility testing demonstrate reversible airway obstruction. Bronchial provocation tests (BPT) measure bronchial hyperresponsiveness. Fractional exhaled nitric oxide (FeNO) indicates airway inflammation. Allergy tests show underlying atopy. Diagnostic algorithms that combine these tests have been proposed recently by the National Institute for Health and Care Excellence (NICE) and the Global Initiative for Asthma (GINA) [1-3]. However, the accuracy of these diagnostic algorithms in school-aged children suspected for asthma is not clear. Uncertainty about the presence of asthma leads to under- or over treatment [3-5]. Systematic literature reviews done as part of the ongoing task force of the European Respiratory Society (ERS) on asthma diagnosis in children found only few relevant studies [1-3]. Murray et al. assessed the diagnostic accuracy of the diagnostic algorithm proposed in the NICE guideline in a population-based study [6]. We recently assessed diagnostic tests in a clinical study of 111 school-aged outpatients referred for suspected asthma and found that accuracy was highest for reported triggers and severity of wheeze, FeNO, and BPT by methacholine or exercise [7]. However, these data came either from the general population, or a research setting and the accuracy of diagnostic tests for asthma has never been formally evaluated in a real-life situation. Especially the diagnostic accuracy of body plethysmography has not been assessed previously. We assessed the diagnostic accuracy of respiratory symptoms, diagnostic tests and two paediatric diagnostic algorithms by GINA and NICE in school-aged children referred with suspected asthma to respiratory outpatient clinics.

Methods

Study population and study design

For this analysis, we used the baseline measurement of the Swiss Paediatric Airway Cohort (SPAC). SPAC is a prospective clinical cohort embedded in routine care [8]. This analysis shows data from children aged 5-17 years invited from July 2017 to June 2019 (Figure 1). They were consecutive referrals with symptoms suggestive of asthma e.g. wheeze, cough, exercise induced breathing problems or dyspnoea reported in the referral letter. We excluded children with missing questionnaire or hospital letter.

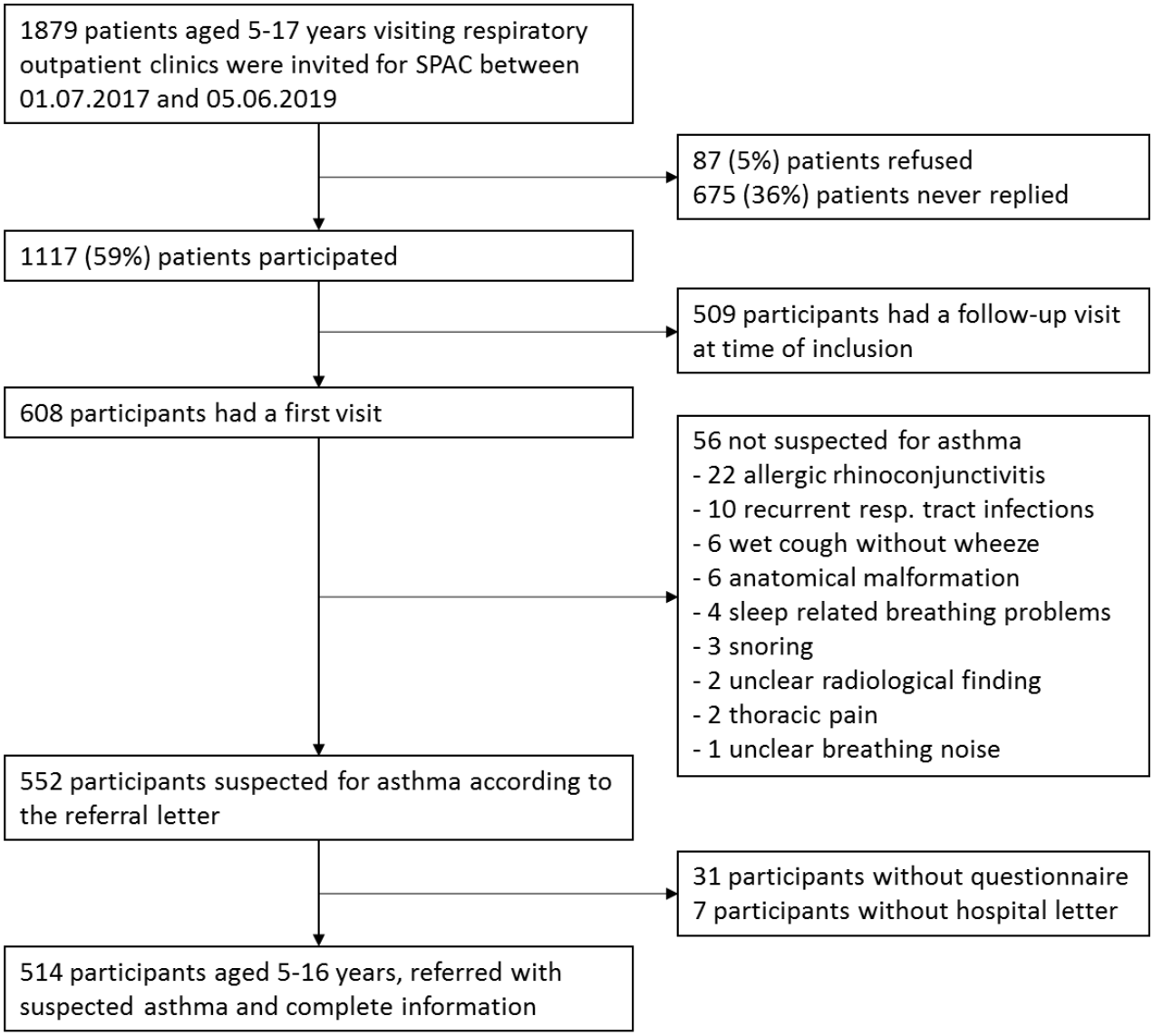


Figure 1 Inclusion of study participants

Study procedures

The families received the parental questionnaire with the invitation letter to attend the clinic or upon arrival at the paediatric respiratory outpatient clinic. At the visit, children underwent clinical evaluation, allergy testing (unless allergy test results were reported in the referral letter), measurement of FeNO, spirometry, body plethysmography and bronchodilator reversibility testing. Where indicated, children also underwent bronchial provocation test by methacholine, exercise or mannitol either during the same visit or at a follow-up visit within 3 months. Ethical approval was obtained from the Bernese ethics committee (KEB 2016-02176) and all participating parents and adolescents aged 14 years or older gave written informed consent.

Clinical asthma diagnosis (reference standard)

The clinical diagnosis (definite asthma, probable asthma or other disease) was the one put down by the experienced paediatric pulmonologist in the letter to the referring primary care physician. The diagnosis was based on medical history, clinical examination, and all tests results. Where the diagnosis was unclear (e.g. described as probable asthma) and a follow-up visit took place within 3 months, we used the clinical diagnosis from the follow-up visit.

Respiratory symptoms and diagnostic tests

The parental questionnaire included key questions for lower respiratory symptoms from the international study of asthma and allergies in childhood (ISAAC) and further detailed questions from the Leicester respiratory cohort questionnaires [9, 10]. All diagnostic tests were performed according to published guidelines [11, 12]. Children were instructed to withhold short acting beta2-agonists for 8 hours, inhaled corticosteroids, leukotriene antagonists, and long acting beta2-agonists for 24 hours, and antihistamines and sodium cromoglycate for >72 hours before the visit.

Skin prick test and specific IgE measurement were used to measure atopy. Skin prick tests were done using histamine, saline and birch, grass, mugwort, alternaria, cat, house dust mites (D. pteronyssinus and farinae)

[13]. A wheal size of ≥3 mm was considered positive in case the positive control (histamine) had a wheal size of ≥3 mm and the negative control (saline) had a wheal size of <3mm. Specific IgE levels for birch, grass, mugwort, alternaria, cat, house dust mites (D. pteronyssinus and farinae) were measured in serum samples using the fluorescence enzyme immunoassay/immunocap (Thermo Fisher Scientific, Uppsala, Sweden). IgE levels were considered positive at the detection threshold (≥0.35 kU/l).

Fractional exhaled nitric oxide (FeNO) was measured in doublets before spirometry, using the portable multi-gas analyser (NIOX MINO®, Aerocrine, Sweden) in St. Gallen and the CLD 88sp (Ecomedics) in Bern, Basel, Aarau and Zurich and Luzern, in accordance with published guidelines [12]. These devices show good agreement [14].

Spirometry and body plethysmography were performed using American Thoracic Society (ATS) criteria for paediatric lung function testing and a Jaeger masterscope (Erich Jaeger GmbH, Würzburg, Germany) using JLAB software (version 4.34) (Basel and St. Gallen) or MasterScreen Pneumo spirometer using Sentrysuite software (Bern, Zurich, Aarau, and Lucerne). Spirometry was done in triplicate by experienced lung function technicians, who performed quality control during the measurement, and recorded the best measurement. The flow-volume curve was checked by the responsible paediatric pulmonologist. Results of the spirometry (forced expiratory volume in 1 second (FEV_1) and forced expiratory flow (FEF) at 50% of the forced vital capacity (FVC)) are expressed as z-scores based on GLI-2012 reference standards [15] and as proportion (FEV_1/FVC). The results of body plethysmography are expressed as kPa·s for the specific effective airway resistance (sReff) and specific total airway resistance (sRtot) and as proportion (residual volume (RV) / total lung capacity (TLC)).

Bronchodilator reversibility test was performed if FEV1 was ≤90%, FEF75 ≤67%, FEF50 ≤67%, or FEF25 ≤67% (Lucerne, Zurich and Aarau), if SReff >180% or FEF50 <80% (Bern), or in all patients (St. Gallen and Basel). All centres gave salbutamol 400 μg (Ventolin® pMDI via spacer) to assess bronchodilator reversibility. Spirometry was repeated in duplicate after 10 (Lucerne and Basel), 15 (St. Gallen, Aarau and Bern) or 20 minutes (Zurich). Bronchodilator reversibility was calculated by the following equation: (post-bronchodilator FEV1–pre-bronchodilator FEV1)x100/pre-bronchodilator FEV1.

Statistical analysis

We calculated sensitivity, specificity, positive predictive value and negative predictive value, Youden's Index (sensitivity + specificity – 1), area under the curve (AUC) and 95% confidence intervals (CI) for the reported symptoms and diagnostic tests to diagnose asthma. The cut-off with the best diagnostic accuracy was the value with the highest Youden's index. We assessed the diagnostic accuracy of tests, if they were done in at least 70% of the children. To assess the diagnostic accuracy of bronchodilator reversibility we did a sub analysis in children with obstructive lung function (FEV1/FVC <80%) [1, 16]. We did a first sensitivity analysis, classifying children with "probable asthma" as having "no asthma". We did a second sensitivity analysis using only steroid naïve children. We applied the asthma diagnosis algorithms by GINA and NICE to assess how they would have performed in a clinical setting and calculated sensitivity, specificity, positive predictive value and negative predictive value. We used STATA software (version 15; College Station, Texas) for statistical analysis.

Results

Characteristics of the study population

Of the 514 children fulfilling the inclusion criteria, 57% were male and the median age was 9 years (table 1). Most of the referred children reported wheeze (62%) and/or cough (55%) (table 1). Of the 514 participants, 356 (69%) were diagnosed with asthma. Exercise related symptoms (15%) and cough (14%) not due to asthma such as inducible laryngeal obstruction or recurrent colds were frequent other diagnoses (table S1).

Table 1. Characteristics of the study participants (N=514)

	Total n (%)	
Age, median [IQR]	9	[7-12]
Sex, male	294	(57)
BMI, median z-score [IQR]	0.3	[-0.4-1.1]
Respiratory symptoms in the last 12 months		
Any wheeze	317	(62)
More than 3 attacks of wheeze	170	(33)
Wheeze with colds	230	(45)
Exercise-induced wheeze	232	(45)
Wheeze triggered by pollen	127	(25)
Wheeze triggered by house dust	81	(16)
Wheeze triggered by pets	64	(12)
Awakening due to wheeze	182	(35)
Cough longer than 4 weeks	214	(42)
Night cough	271	(53)
Cough more than others	281	(55)
Dyspnoea	230	(45)
Inhalation medication in the last 12 months		
Any	395	(77)
Short-acting B2-agonist, alone	152	(30)
ICS +/- Short-acting B2-agonist	114	(22)
ICS + Long-acting B2-agonist	129	(25)

IQR: inter quartile range, BMI: body mass index, ICS: inhaled corticosteroids

Diagnostic accuracy of respiratory symptoms to diagnose asthma

Any reported wheeze in the past 12 months had the highest sensitivity (74%) and Youden's Index (0.39) for asthma (table 2). Specificity was highest for frequent attacks (>3/year) (84%), awakening due to wheeze (82%) and wheeze triggered by pollen (92%), house dust (97%) or pets (97%). Youden's Index was also relatively high for wheeze triggered by colds (0.36) or exercise (0.30) and dyspnoea (0.31).

Table 2. Diagnostic accuracy of respiratory symptoms to diagnose asthma (N=514)

	A+S+ n	**A-S+** n	**A+S-** n	**A-S-** n	**Sens** % (95%CI)	**Spec** % (95%CI)	**PPV** % (95%CI)	**NPV** % (95%CI)	**YI**
Respiratory symptoms in the past 12 months									
Any wheeze	262	55	90	100	74 (70-79)	65 (56-72)	83 (78-87)	53 (45-60)	0.39
> 3 attacks of wheeze	145	25	200	129	42 (37-47)	84 (77-89)	85 (79-90)	39 (34-45)	0.26
Wheeze with colds	196	34	141	120	58 (53-63)	78 (71-84)	85 (80-90)	46 (40-52)	0.36
Exercise-induced wheeze	192	40	154	115	55 (50-61)	74 (67-81)	83 (77-87)	43 (37-49)	0.30
Wheeze triggered by									
Pollen	115	12	227	145	34 (29-39)	92 (87-96)	91 (84-95)	39 (34-44)	0.26
House dust	76	5	259	150	23 (18-28)	97 (93-99)	94 (86-98)	37 (32-42)	0.19
Pets	59	5	274	152	18 (14-22)	97 (93-99)	92 (83-97)	36 (31-40)	0.15
Awakening due to wheeze	155	27	191	127	45 (39-50)	82 (76-88)	85 (79-90)	40 (35-46)	0.27
Cough > 4 weeks	140	74	209	81	40 (35-45)	52 (44-60)	65 (59-72)	28 (23-33)	-0.08
Night cough	189	82	153	74	55 (50-61)	47 (39-56)	70 (64-75)	33 (27-39)	0.03
Cough more than others	200	81	146	70	58 (52-63)	46 (38-55)	71 (65-76)	32 (26-39)	0.04
Dyspnoea	192	38	154	116	55 (50-61)	75 (68-82)	83 (78-88)	43 (37-49)	0.31

A+S+: children with asthma diagnosis and reported symptom, A-S+: children without asthma diagnosis but with symptom, A+S-: children with asthma diagnosis but without symptom, A-S-: children without asthma and without symptom, Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value YI: Youden's-Index: Sensitivity + Specificity -1

Diagnostic accuracy of tests to diagnose asthma

The tests done in each centre and their results are shown in table S2 and table S3. Allergy tests were performed in 467 (91%) of the 514 children. FeNO was performed in 501 (97%), spirometry in 514 (100%), body plethysmography in 432 (84%), and bronchodilator reversibility in 381 children (74%). We excluded 63, 19, 45, and 15 measurements, respectively, because of poor quality. The accuracy of bronchial provocation tests was not assessed, because it was only done in 210 (41%) children.

The cut-off values with the best diagnostic accuracy were ≥1 positive test for the allergy test, ≥23ppb for FeNO, ≤-0.7 z-score for FEV1, <84% for FEV1/FVC, ≤-0.3 z-score for FEF50, ≥0.9 kPa·s for sReff, ≥1.1 kPa·s for sRtot, ≥25% for RV/TLC and ≥7% increase in FEV1 for the bronchodilator reversibility test (table 3). The diagnostic accuracy (area under the curve) was highest for sRtot (0.74), allergy test (0.70), FEF50 (0.69) and FeNO (0.68). The accuracy was lowest for RV/TLC (0.56) and bronchodilator reversibility test (0.60). However, bronchodilator reversibility test had highest accuracy (0.75) when we analysed children with FEV1/FVC <80% (figure 2).

Table 3. Diagnostic accuracy of diagnostic tests to diagnose asthma N=514

	A+T+ n	A-T+ n	A+T- n	A-T- n	Sens % (95%CI)	Spec % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	YI	AUC
Clinical tests										
Allergy test[1]										0.70
≥1 positive test*	260	52	81	74	76 (71-81)	59 (50-67)	83 (79-87)	48 (40-56)	0.35	
≥2 positive tests	199	34	142	92	58 (53-64)	73 (64-81)	85 (80-90)	39 (33-46)	0.31	
FeNO										0.68
≥20ppb	157	31	147	103	52 (46-57)	77 (69-84)	84 (77-89)	41 (35-48)	0.29	
≥21ppb	153	27	151	107	50 (45-56)	80 (72-86)	85 (79-90)	41 (35-48)	0.30	
≥23ppb*	145	18	159	116	48 (42-53)	87 (80-92)	89 (83-93)	42 (36-48)	0.34	
≥25ppb	139	16	165	118	46 (40-52)	88 (81-93)	90 (84-94)	42 (36-48)	0.34	
Spirometry										
FEV1										0.66
≤-0.7 z-score*	148	30	195	121	43 (38-49)	80 (73-86)	83 (77-88)	38 (33-44)	0.23	
≤-1.0 z-score	109	23	234	128	32 (27-37)	85 (78-90)	83 (75-89)	35 (30-41)	0.17	
FEV1/FVC										0.65
<80%	120	15	216	128	36 (31-41)	90 (83-94)	89 (82-94)	37 (32-43)	0.25	
<84%*	174	33	162	110	52 (46-57)	77 (69-84)	84 (78-89)	40 (35-47)	0.29	
<90%	245	84	91	59	73 (68-78)	41 (33-50)	74 (69-79)	39 (31-48)	0.14	
FEF50										0.69
≤-0.3 z-score*	171	31	122	93	58 (52-64)	75 (66-82)	85 (79-89)	43 (37-50)	0.33	
≤-1.0 z-score	96	13	197	111	33 (27-38)	90 (83-94)	88 (80-93)	36 (31-42)	0.22	
Bodyplethysm.										
sReff[2]										0.66
≥0.9 kPa·s/l*	118	25	114	76	51 (44-57)	75 (66-83)	83 (75-88)	40 (33-47)	0.26	
≥1.0 kPa·s/l	96	18	136	83	41 (35-48)	82 (73-89)	84 (76-90)	38 (31-45)	0.24	
sRtot[3]										0.74
≥1.0 kPa·s/l	35	11	4	6	90 (76-97)	35 (14-62)	76 (61-87)	60 (26-88)	0.25	
≥1.1 kPa·s/l *	32	7	7	10	82 (66-92)	59 (33-82)	82 (66-92)	59 (33-82)	0.41	
RV/TLC										0.56
≥25%*	204	80	61	36	77 (71-82)	31 (23-40)	72 (66-77)	37 (28-48)	0.08	
Bronchodilator rev.										0.60
FEV_1										
≥7% increase*	188	43	86	49	69 (63-74)	53 (43-64)	81 (76-86)	36 (28-45)	0.22	
≥10% increase	160	37	114	55	58 (52-64)	60 (49-70)	81 (75-86)	33 (26-40)	0.18	
≥12% increase	145	34	129	58	53 (47-59)	63 (52-73)	81 (74-86)	31 (24-38)	0.16	
Bronchodilator rev.										0.75
if FEV1/FVC <80%[4]										
≥7% increase*	89	4	23	9	79 (71-87)	69 (39-91)	96 (89-99)	28 (14-47)	0.49	
≥10% increase	73	3	39	10	65 (56-74)	77 (46-95)	96 (89-99)	20 (10-34)	0.42	
≥12% increase	65	2	47	11	58 (48-67)	85 (55-98)	97 (90-99)	19 (10-31)	0.43	

A+T+: children with asthma diagnosis and positive test result, A-T+: children without asthma diagnosis but positive test result, A+T-: children with asthma diagnosis but negative test result, A-T-: children without asthma and negative test result, Sens: sensitivity, Spec: specificity, PPV: positive predictive value, NPV: negative predictive value, YI: Youden's-Index: Sensitivity + Specificity -1, AUC: area under the curve, FeNO: fractional exhaled nitric oxide, ppb: parts per billion, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, FEF50: forced expiratory flow at 50% of FVC, sReff: specific effective airway resistance, sRtot: specific total airway resistance, RV: residual volume, TLC: total lung capacity, Bronchodilator rev.: bronchodilator reversibility

Displayed cut-offs chosen based on proposed cut-offs from previous publications

*Cut-off with maximum combined sensitivity and specificity (highest Youden's-Index)

[1] Number allergens for which the skin prick test is positive: wheal size ≥3 or the specific IgE test was positive: ≥0.35 kU/l.

[2] Reported by 4 centres

[3] Reported by 2 centres

[4] N= 126, cut-off chosen based on proposed cut-off from previous publications and guidelines

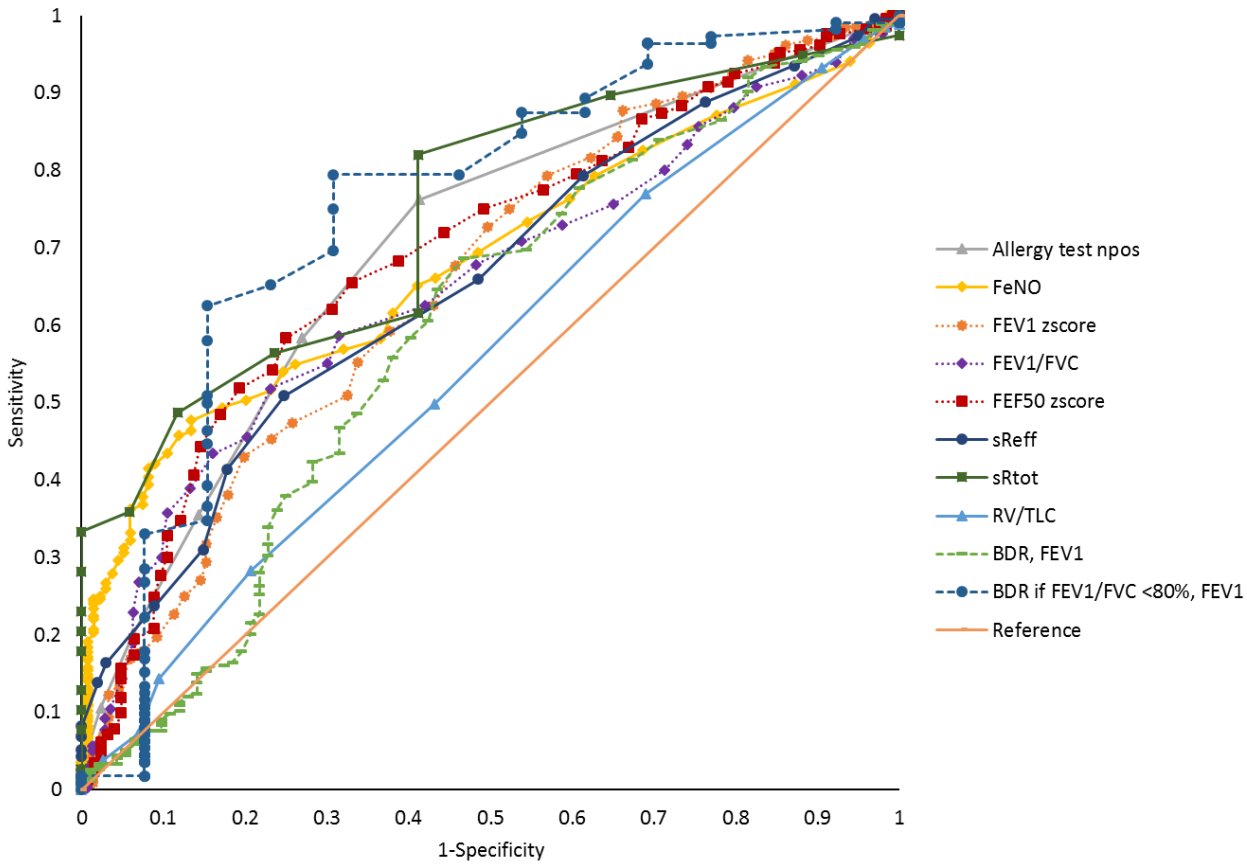


Figure 2 Receiver operating characteristics (ROC) curve of clinical tests to diagnose asthma.

Test	**Unit**
Allergy test	increase of 1 positive skin prick or specific IgE test
FeNO	increase of 1 parts per billion (ppb)
FEV1	increase of 0.1 z-score
FEV1/FVC	increase of 1%
FEF75	increase of 0.1 z-score
sReff	decrease of 0.01 kPa·s
sRtot	decrease of 0.01 kPa·s
RV/TLC	increase of 5%
Bronchodilator reversibility (BDR), FEV_1	increase of 1% in FEV_1

Sensitivity analysis

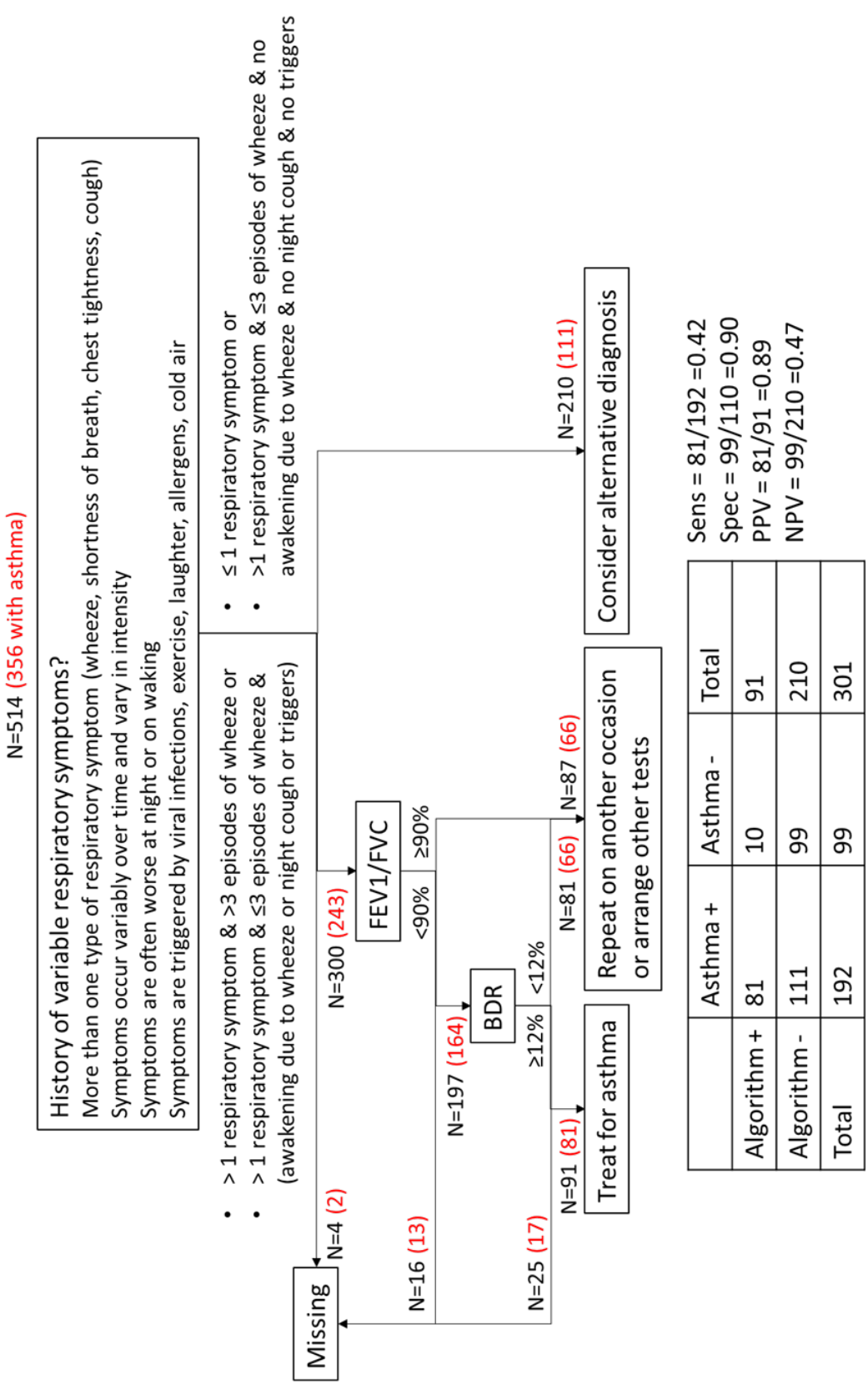
In the first sensitivity analysis, where we classified children with "probable asthma" as having "no asthma", the cut-offs with highest combined sensitivity and specificity only changed slightly for FEV1 (from ≤-0.7 z-score to ≤-0.2 z-score) and FEF50 (from ≤-0.3 z-score to ≤-0.5 z-score). The diagnostic accuracy (area under the curve) remained highest for FEF50 (0.73) and FeNO (0.70) and increased for FEV1/FVC (from 0.65 to 0.72), and sReff (from 0.66 to 0.68). The accuracy remained lowest for RV/TLC (0.53) and bronchodilator reversibility test (0.60) (table s4).

In the second sensitivity analysis, which included only ICS naïve children, asthma was diagnosed in 156 (58%) of the 271 children (table s5). The cut-offs with highest combined sensitivity and specificity changed for FeNO (from ≤23 ppb to ≤28 ppb), FEV1/FVC (from 84% to 86%), sRtot (from 1.1 kPa·s to 1.5 kPa·s) and RV/TLC (from ≥25% to ≥35%). The diagnostic accuracy remained highest for sRtot (0.77), allergy test (0.71), FEF50 (0.70) and FeNO (0.71), as in the main analysis. The accuracy was still lowest for RV/TLC (0.51) and bronchodilator reversibility test (0.56) (table S6).

Diagnostic accuracy of algorithms to diagnose asthma

We applied the GINA diagnostic algorithm to the 514 children suspected for asthma. We were able to pass 91 children through until the step "treat for asthma" (figure 3). Of these, 81 (positive predictive value (PPV) 89%) were diagnosed with asthma by the paediatric pulmonologist. Of the 210 children who we could pass through until the step "consider alternative diagnosis", 111 were diagnosed with asthma, and 99 (negative predictive value (NPV) 47%) were not. The sensitivity of the algorithm was 42% and the specificity was 90%. In 168 children the GINA algorithm would have been inconclusive, because they ended at the step "repeat on another occasion or arrange other tests". Of these 132 were diagnosed with asthma by the paediatric pulmonologists in our study.

We applied the NICE diagnostic algorithm to the 514 children suspected for asthma. We were able to pass 38 children through until the step "diagnose asthma" (figure S2). Of these 38 children, 35 (PPV 92%) were diagnosed with asthma by the paediatric pulmonologists. Of the 22 children who we could pass through until the step "refer for specialist assessment", 18 were diagnosed with asthma and 6 (NPV 27%) were not. The sensitivity was 69% and the specificity was 67%. However, 362 (83%) children would pass through until the step "2 weeks of PEF monitoring". From this step on wards we could not apply the NICE diagnostic algorithm.



	Asthma +	Asthma -	Total
Algorithm +	81	10	91
Algorithm -	111	99	210
Total	192	99	301

Figure 3 Diagnostic accuracy of the diagnostic algorithm from the GINA guideline

Number in black: number of patients at this step. Number in red: number of patients with doctor diagnosed asthma at this step. Algorithm +: treat for asthma. Algorithm -: consider alternative diagnosis. FEV1: forced expiratory volume in 1 second. FVC: forced vital capacity. BDR: bronchodilator reversibility

*168 patients would need to repeat the spirometry and bronchodilator reversibility measurement or bronchial provocation test during another visit.

Discussion

This study, embedded in routine care, found that the currently used tests alone, or their combination as suggested by GINA or NICE algorithms, are not very helpful to diagnose asthma in a clinical setting. The paediatric diagnostic algorithm by GINA was specific (90%), but not sensitive (42%) and the NICE algorithm depends very much on 2 weeks PEF monitoring, which should have been done in 83% of children, according to the algorithm. This not practical for an outpatient setting. We found that the combined sensitivity and specificity to diagnose asthma in our study was highest for any wheeze ((sensitivity/specificity) 74/65) and the diagnostic accuracy (area under the curve) was highest for sRtot (0.74), a positive allergy test (0.70), FEF50 (0.69), FeNO (0.68) and bronchodilator reversibility test in children with FEV1/FVC <80% (0.75) and lowest for RV/TLC (0.56).

To our knowledge, this is the first study assessing diagnostic accuracy of body plethysmography and the largest study assessing this for respiratory symptoms, diagnostic tests and algorithms to diagnose asthma in routine care. Only few other studies have assessed the accuracy of symptoms and tests in school-aged children consecutively referred for evaluation of possible asthma [7, 17-19]. They all found that reported wheeze was sensitive (ranging 75-86%) but not specific (64-73%) and that frequent wheeze and awakening due to dyspnoea were specific (84-90%) but not sensitive (33-54%), which is in line with our findings. In our previous study in a different clinical population, the combined sensitivities and specificities were highest for the same symptoms. In the current study also wheeze with colds and dyspnoea scored high [7]. As reported by Woo et al. and our previous study, we confirmed that a positive skin prick test was sensitive (68-90%) but not specific (32-40%) [20]. Most children in our study were allergic (61%), especially those with asthma (73%). There is an ongoing discussion on the place of allergy tests in the diagnosis of asthma, some suggest that it rather distinguishes subtypes [21, 22]. The area under the curve (AUC) for FeNO in our study (0.68) was lower than in our previous study (0.79) and in a Korean study by Eom et al. (0.80). [7, 23] FEV1/FVC had low diagnostic accuracy in all studies. FEF25-75 (0.81) and FEF50 (0.69) seem to perform better. Differences

between AUCs between the Korean study and ours could be due to their exclusion of the children with unclear asthma.

The accuracy of the diagnostic algorithm by GINA has not been studied previously. The specificity was with 90% relatively high, but this would still lead to 10% over diagnosis of asthma. The sensitivity was only 42%, which means that the GINA algorithm cannot exclude asthma. The NICE algorithm has previously been tested using data from the Manchester Asthma and Allergy Study, a population-based cohort of 1184 children aged 13-16 years, of which 89 were symptomatic but not regularly inhaling corticosteroids [6]. They found that less stringent cut off values had higher sensitivity and specificity than those proposed in the algorithm. However, the Manchester study used parent-reported data to define asthma (wheeze and asthma treatment in the past 12 months plus a doctor diagnosis of asthma ever in life) and compared them to healthy children, excluding from the analysis all those with possible asthma. In clinical practice, we want to distinguish children with asthma from those with respiratory symptoms due to other causes, not from healthy children. In our clinical population, only 38 children out of 514 could be diagnosed with asthma based on the NICE algorithm (FEV1/FVC <70% and bronchodilator responsibility of ≥12%). Nearly all (83%) would have needed additional 2 weeks peak expiratory flow monitoring followed by a second visit to the outpatient clinic (Figure S2). Besides that this test is not used in most countries, it would also not be practical for a busy outpatient clinic. We also found less stringent cut off values to have high sensitivity and specificity compared to the values used in the NICE algorithm (FEV1/FVC <84% vs. <70%, bronchodilator reversibility ≥7% vs. ≥12% and FeNO ≥23ppb vs. ≥35ppb, respectively). In fact, the cut-off values proposed by NICE are derived from studies on adults, not children.

The main strength is that this study was embedded in routine care and we included the whole spectrum of children newly referred with suspected asthma to paediatric respiratory outpatient clinics. In a sensitivity analysis, we restricted to a steroid-naïve population. Because of the parental questionnaire, we had detailed information on respiratory symptoms. We also could assess the diagnostic accuracy of body plethysmography, which has not been done before.

A main weakness of this study, which however is unavoidable, is that the reference standard for asthma diagnosis (the physicians' diagnosis) took into account the results of the patient history and diagnostic tests for which the accuracy was assessed. However, given the lack of a stand-alone diagnostic test for asthma, the physicians diagnosis based on the history, physical examination and diagnostic test results is closest to the true diagnosis [1, 24, 25]. The multicentre study adds heterogeneity in the tests and diagnoses, but increases generalisability of the findings. Some tests were not done in all children. This could have introduced a selection bias, because the children who were tested could differ from those who were not. However, the percentage not tested was low so the potential impact on the results is small, because we only evaluated tests done in more than 70% of the children.

Our findings highlight the need for better diagnostic algorithms combining respiratory symptoms and objective tests to diagnose asthma. It also highlights the need to base these diagnostic algorithms on clinical studies in the appropriate age group to generate evidence of the value of different tests for the diagnosis of asthma in children. Our findings suggest that the cut-offs used in the NICE algorithm derived from adults are indeed not useful for children. Future studies should ideally assess respiratory symptoms, allergy, FeNO, spirometry, body plethysmography and bronchodilator reversibility tests in all children and use a systematic approach to develop an accurate diagnostic algorithm combining these tests.

Currently, asthma diagnosis seems not straightforward as there is no common way to diagnose asthma even for experienced pulmonologist, which highlights the need for new evidence-based guidance.

Acknowledgements

We thank all participants in the Swiss Paediatric Airway Cohort, lab technicians and doctors of the pulmonology divisions in the children's hospitals of Aarau, Basel, Bern, Chur, Lucerne, St. Gallen and Zurich for their assistance in the study. We thank Christopher Ritter for his editorial assistance.

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Supplementary material

Table S1. Diagnoses in children with suspected asthma after visiting the clinic* N=514

	Diagnoses n (%)	
Definite diagnoses		
Asthma	259	(50)
Cough not due to asthma[1]	71	(14)
Exercise related symptoms not due to asthma[2]	56	(11)
Allergic rhino conjunctivitis	11	(2)
Non-CF bronchiectasis	1	(<1)
Probable diagnoses		
Asthma	97	(19)
Exercise related symptoms not due to asthma[2]	19	(4)

*Diagnosis at the first visit at a follow up visit within 3 months if the diagnosis was unclear

[1] Recurrent colds, post infectious cough, habitual cough, etc.

[2] Inducible laryngeal obstruction, dysfunctional breathing, functional symptoms, etc.

Table S2. Proportion of patients who performed diagnostic tests* per centre N=514

	Centres						**Total**
	A	B	C	D	E	F	
	N=60	N=196	N=83	N=75	N=15	N=85	N=514
Diagnostic tests	n%	n%	n%	n%	n%	n%	n%
Any allergy test[1]	60 (100)	182 (93)	74 (89)	55 (73)	15 (100)	81 (95)	467 (91)
FeNO	60 (100)	185 (94)	81 (98)	75 (100)	15 (100)	85 (100)	501 (97)
Spirometry	60 (100)	196 (100)	83 (100)	75 (100)	15 (100)	85 (100)	514 (100)
Body plethysmography	59 (98)	171 (87)	52 (63)	61 (81)	10 (67)	79 (93)	432 (84)
Bronchodilator reversibility	29 (48)	145 (74)	61 (73)	68 (91)	15 (100)	63 (74)	381 (74)
Any bronchial provocation test	13 (22)	86 (44)	23 (28)	23 (31)	7 (47)	58 (68)	210 (41)
Methacholine	7 (12)	71 (36)	2 (2)	1 (1)	-	48 (56)	129 (25)
Exercise	7 (12)	18 (9)	21 (25)	22 (29)	5 (33)	12 (14)	85 (17)
Mannitol	-	-	-	-	3 (20)	-	3 (1)

*At the first visit or at a follow up visit within 3 months

[1]Allergy test either done as above or results from <6 months ago reported in referral letter.

Table S3. Diagnostic test results in patients with and without asthma N=514

	Asthma					
	Definite asthma N=259		**Probable asthma** N=97		**Other diagnosis** N=158	
Diagnostic tests	median (IQR)		median (IQR)		median (IQR)	
Any allergy test, n(%)	248	(96)	93	(95)	124	(79)
≥1 positive test n(%)	201	(74)	59	(61)	52	(36)
Number of positive tests[1]	2	(1-3)	1	(0-3)	0	(0-2)
FeNO, n(%)	227	(88)	77	(80)	134	(84)
Parts per billion	25	(12-50)	14	(8-28)	11	(7-18)
Spirometry, n(%)	253	(98)	90	(93)	152	(96)
FEV1, z-scores	-0.5	(-1.4-0.1)	-0.2	(-1.0-0.5)	0.1	(-0.6-0.8)
FEV1/FVC	82	(76-88)	90	(84-95)	88	(84-93)
FEF50, z-score	-0.8	(-1.4--0.1)	0.1	(-0.7-0.9)	0.2	(-0.4-0.9)
Bodyplethysmography, n(%)	197	(76)	73	(75)	117	(74)
sReff, kPa·s[2]	1.0	(0.8-1.3)	0.8	(0.7-0.9)	0.8	(0.6-0.9)
sRtot, kPa·s[3]	1.3	(1.1-1.8)	1.4	(1.3-1.5)	1.1	(1.0-1.3)
RV/TLC	30	(25-36)	30	(26-36)	29	(24-34)
Bronchodilator reversibility, n(%)	215	(83)	59	(60)	92	(59)
Increase in FEV1 in %	13	(6-25)	10	(1-26)	6	(2-18)

[1]Defined as wheal size ≥3mm for mites, cat, grass, birch, mugwort and alternaria skin prick test and as ≥0.35kU/L for specific IgE test

[2] Reported by 4 centres

[3] Reported by 2 centres

Table S4. Diagnostic accuracy of diagnostic tests to diagnose asthma N=514 (sensitivity analysis: asthma is defined as definite asthma and not asthma is defined as probable asthma or other diagnosis)

	A+T+ n	A-T+ n	A+T- n	A-T- n	Sens % (95%CI)	Spec % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	YI	AUC
Clinical tests										
Allergy test[1]										0.67
≥1 positive test*	201	111	47	108	81 (76-86)	49 (43-56)	64 (59-70)	70 (62-77)	0.30	
≥2 positive tests	154	79	94	140	62 (56-68)	64 (57-70)	66 (60-72)	60 (53-66)	0.26	
FeNO										0.70
≥20ppb	130	58	97	153	58 (51-64)	73 (66-78)	69 (62-76)	61 (55-67)	0.30	
≥21ppb	127	53	100	158	56 (49-63)	75 (68-81)	71 (63-77)	61 (55-67)	0.31	
≥23ppb*	119	44	108	167	52 (46-59)	79 (73-84)	73 (66-80)	61 (55-67)	0.32	
≥25ppb	114	41	113	170	50 (44-57)	81 (75-86)	74 (66-80)	60 (54-66)	0.31	
Spirometry										
FEV1										0.64
≤-0.2 z-score*	159	102	94	139	63 (57-69)	58 (51-64)	61 (55-67)	60 (53-66)	0.21	
≤-0.7 z-score	111	67	142	174	44 (38-50)	72 (66-78)	62 (55-69)	55 (49-61)	0.16	
≤-1.0 z-score	87	45	166	196	34 (29-41)	81 (76-86)	66 (57-74)	54 (49-59)	0.16	
FEV1/FVC										0.72
<80%	107	28	141	203	43 (37-50)	88 (83-92)	79 (71-86)	59 (54-64)	0.31	
<84%*	153	54	95	177	62 (55-68)	77 (71-82)	74 (67-80)	65 (59-71)	0.38	
<90%	202	127	46	104	81 (76-86)	45 (38-52)	61 (56-67)	69 (61-77)	0.26	
FEF50										0.73
≤-0.5 z-score*	131	46	87	155	60 (53-67)	77 (71-83)	74 (67-80)	64 (58-70)	0.37	
≤-1.0 z-score	83	27	135	174	38 (32-45)	87 (81-91)	75 (66-83)	56 (51-62)	0.25	
Bodyplethysm.										
sReff										0.68
≥0.9 kPa·s*	98	45	68	122	59 (51-67)	73 (66-80)	69 (60-76)	64 (57-71)	0.32	
≥1.0 kPa·s	81	33	85	134	49 (41-57)	80 (73-86)	71 (62-79)	61 (54-68)	0.29	
sRtot										0.64
≥1.0 kPa·s	28	18	4	6	88 (71-96)	25 (10-47)	61 (45-75)	60 (26-88)	0.13	
≥1.1 kPa·s *	25	14	7	10	78 (60-91)	42 (22-63)	64 (47-79)	59 (33-82)	0.20	
RV/TLC										0.53
≥25%*	150	134	45	52	77 (70-83)	28 (22-35)	53 (47-59)	54 (43-64)	0.05	
Bronchodilator rev.										0.60
FEV_1										
≥7% increase*	156	75	59	76	73 (66-78)	50 (42-59)	68 (61-74)	56 (47-65)	0.23	
≥10% increase	131	66	84	85	61 (54-67)	56 (48-64)	66 (59-73)	50 (43-58)	0.17	
≥12% increase	117	62	98	89	54 (48-61)	59 (51-67)	65 (58-72)	48 (40-55)	0.13	

A+T+ = children with asthma diagnosis and positive test result, A-T+ = children without asthma diagnosis but positive test result, A+T- = children with asthma diagnosis but negative test result, A-T- = children without asthma and negative test result, Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value, YI = Youden's-Index = Sensitivity + Specificity -1, AUC = area under the curve, FeNO = fractional exhaled nitric oxide, ppb = parts per billion, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, FEF50 = forced expiratory flow at 50% of FVC, sReff = specific effective airway resistance, sRtot = specific total airway resistance, RV = residual volume, TLC = total lung capacity, Bronchodilator rev. = bronchodilator reversibility

Cut-offs chosen based on proposed cut-offs from previous publications

*Cut-off with maximum combined sensitivity and specificity (highest Youden's-Index)

[1] Number allergens for which the skin prick test is positive: wheal size ≥3 or the specific IgE test was positive: ≥0.35 kU/l.

[2] Reported by 4 centres

[3] Reported by 2 centres

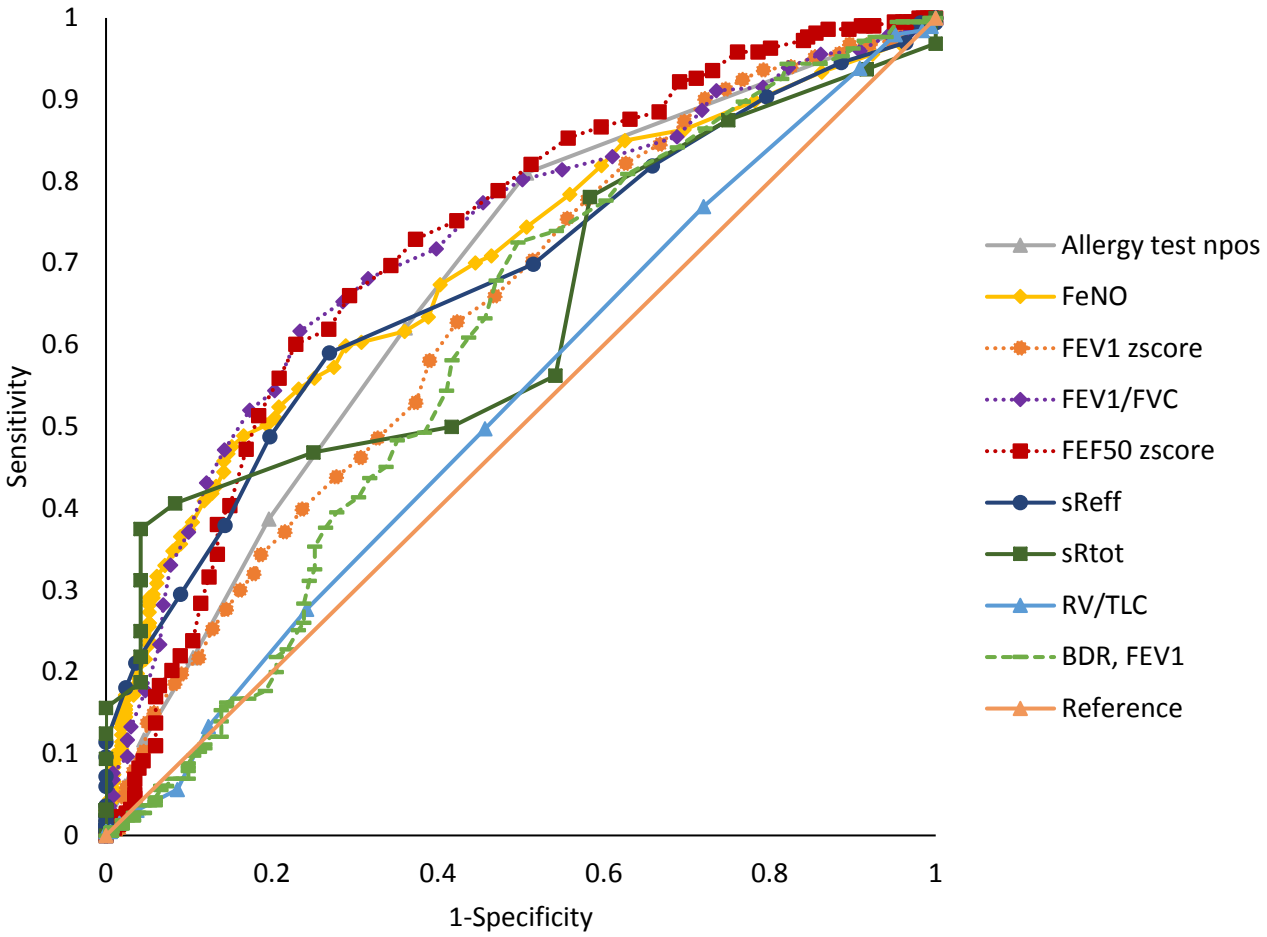


Figure S1 Receiver operating characteristics (ROC) curve of clinical tests to diagnose asthma. (Sensitivity analysis: asthma is defined as definite asthma and not asthma is defined as probable asthma or other diagnosis)

* Cut-off with maximum combined sensitivity and specificity

Test	**Unit**
Allergy test	increase of 1 positive skin prick or specific IgE test
FeNO	increase of 1 parts per billion (ppb)
FEV1	increase of 0.1 z-score
FEV1/FVC	increase of 1%
FEF75	increase of 0.1 z-score
sReff	decrease of 0.01 kPa·s
sRtot	decrease of 0.01 kPa·s
RV/TLC	increase of 5%
Bronchodilator reversibility (BDR), FEV_1	increase of 1% in FEV_1

Table S5. Diagnostic test results in steroid naive patients with and without asthma N=271

	Asthma					
	Definite asthma N=108		**Probable asthma** N=48		**Other diagnosis** N=115	
Diagnostic tests	median (IQR)		median (IQR)		median (IQR)	
Any allergy test, n(%)	101	(94)	46	(96)	86	(75)
≥1 positive test n(%)	87	(81)	31	(65)	39	(34)
Number of positive tests[1]	2	(1-4)	1	(0-3)	0	(0-2)
FeNO, n(%)	90	(83)	42	(88)	98	(85)
Parts per billion	33	(13-54)	17	(8-31)	13	(7-20)
Spirometry, n(%)	102	(94)	46	(96)	112	(97)
FEV1, z-scores	-0.5	(-1.3-0.1)	-0.1	(-1.0-0.5)	0.1	(-0.6-0.9)
FEV1/FVC	82	(77-88)	89	(83-92)	89	(86-95)
FEF50, z-score	-0.7	(-1.4-0.1)	0.1	(-0.7-0.9)	0.2	(-0.2-0.9)
Bodyplethysmography, n(%)	80	(74)	36	(75)	88	(77)
sReff, kPa·s[2]	1.0	(0.7-1.3)	0.8	(0.7-0.9)	0.8	(0.6-0.9)
sRtot, kPa·s[3]	1.3	(1.1-2.3)	1.4	(1.3-1.5)	1.0	(1.0-1.2)
RV/TLC	28	(24-33)	29	(25-37)	30	(24-34)
Bronchodilator reversibility, n(%)	85	(79)	30	(63)	66	(57)
Increase in FEV1 in %	13	(6-25)	5	(2-19)	7	(2-28)

[1]Defined as wheal size ≥3mm for mites, cat, grass, birch, mugwort and alternaria skin prick test and as ≥0.35kU/L for specific IgE test

[2] Reported by 4 centres

[3] Reported by 2 centres

Table S6. Diagnostic accuracy of diagnostic tests to diagnose asthma N=271 (sensitivity analysis: in steroid naïve children)

	A+T+ n	A-T+ n	A+T- n	A-T- n	Sens % (95%CI)	Spec % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	YI	AUC
Clinical tests										
Allergy test[1]										0.71
≥1 positive test*	118	39	29	47	80 (73-86)	55 (44-65)	75 (68-82)	62 (50-73)	0.35	
≥2 positive tests	90	26	57	60	61 (53-69)	70 (59-79)	78 (69-85)	51 (42-61)	0.31	
FeNO										0.71
≥20ppb	75	25	57	73	57 (48-65)	74 (65-83)	75 (65-83)	56 (47-65)	0.31	
≥21ppb	72	23	60	75	55 (46-63)	77 (67-85)	76 (66-84)	56 (47-64)	0.31	
≥23ppb	69	17	63	81	52 (43-51)	83 (74-90)	80 (70-88)	56 (48-64)	0.35	
≥25ppb	66	15	66	83	50 (41-59)	85 (76-91)	81 (71-89)	56 (47-64)	0.35	
≥28ppb*	62	11	70	87	47 (38-56)	89 (81-94)	85 (75-92)	55 (47-63)	0.36	
Spirometry										
FEV1										0.65
≤-0.2 z-score	83	44	65	68	56 (48-64)	61 (51-70)	65 (56-74)	51 (42-60)	0.17	
≤-0.7 z-score*	60	23	88	89	41 (33-49)	79 (71-87)	72 (61-82)	50 (43-58)	0.20	
≤-1.0 z-score	42	17	106	95	28 (21-36)	85 (77-91)	71 (58-82)	47 (40-54)	0.13	
FEV1/FVC										0.69
<80%	47	6	100	99	32 (25-40)	94 (88-98)	87 (77-96)	50 (43-57)	0.26	
<86%*	88	26	59	79	60 (51-68)	75 (66-83)	77 (68-85)	57 (49-66)	0.35	
<90%	109	58	38	47	74 (66-81)	45 (35-56)	65 (58-72)	55 (44-66)	0.19	
FEF50										0.70
≤-0.3 z-score*	70	18	61	77	53 (45-62)	81 (72-88)	80 (70-87)	56 (47-64)	0.34	
≤-1.0 z-score	40	5	91	90	31 (23-39)	95 (88-98)	89 (76-96)	50 (42-57)	0.25	
Bodyplethysm.										
sReff										0.62
≥0.9 kPa·s*	47	20	54	55	47 (37-57)	73 (62-83)	70 (58-81)	50 (41-60)	0.20	
≥1.0 kPa·s	37	15	64	60	37 (27-47)	80 (69-88)	71 (57-83)	48 (39-58)	0.17	
sRtot										0.77
≥1.0 kPa·s	13	7	2	6	87 (60-98)	46 (19-75)	65 (41-85)	75 (35-97)	0.33	
≥1.5 kPa·s *	13	4	2	9	87 (60-98)	69 (39-91)	76 (50-93)	82 (48-98)	0.56	
RV/TLC										0.51
≥35%*	25	17	88	69	22 (15-31)	80 (70-88)	60 (43-74)	44 (36-52)	0.02	
Bronchodilator rev.										
FEV_1										0.56
≥7% increase*	75	32	40	34	65 (56-74)	52 (39-64)	70 (60-79)	46 (34-58)	0.17	
≥10% increase	66	27	49	39	57 (48-67)	59 (46-71)	71 (61-80)	44 (34-55)	0.16	
≥12% increase	59	25	56	41	51 (42-61)	62 (49-74)	70 (59-80)	42 (32-53)	0.13	

A+T+ = children with asthma diagnosis and positive test result, A-T+ = children without asthma diagnosis but positive test result, A+T- = children with asthma diagnosis but negative test result, A-T- = children without asthma and negative test result, Sens = sensitivity, Spec = specificity, PPV = positive predictive value, NPV = negative predictive value, YI = Youden's-Index = Sensitivity + Specificity -1, AUC = area under the curve, FeNO = fractional exhaled nitric oxide, ppb = parts per billion, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, FEF50 = forced expiratory flow at 50% of FVC, sReff = specific effective airway resistance, sRtot = specific total airway resistance, RV = residual volume, TLC = total lung capacity, Bronchodilator rev. = bronchodilator reversibility

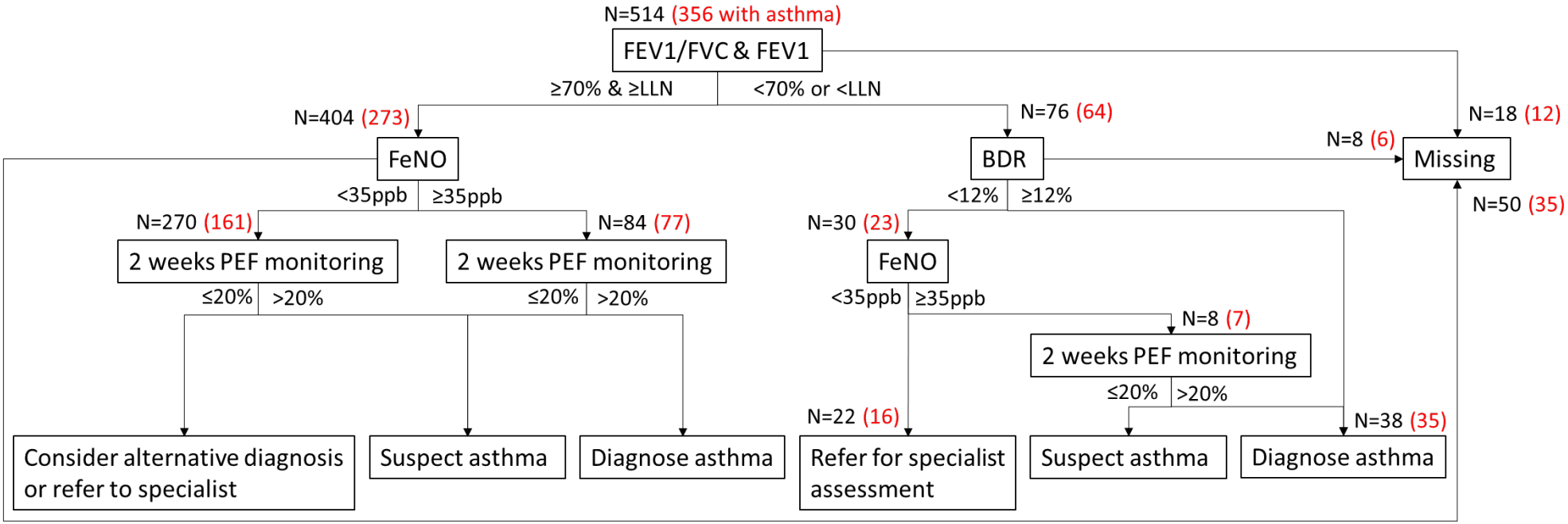
Cut-offs chosen based on proposed cut-offs from previous publications

*Cut-off with maximum combined sensitivity and specificity (highest Youden's-Index)

[1] Number allergens for which the skin prick test is positive: wheal size ≥3 or the specific IgE test was positive: ≥0.35 kU/l.

[2] Reported by 4 centres

[3] Reported by 2 centres



	Asthma +	Asthma -	Total
Algorithm +	35	3	38
Algorithm -	16	6	22
Total	51	9	60

Sens = 35/51 =0.69
Spec = 6/9 =0.67
PPV = 35/38 =0.92
NPV = 6/22=0.27

Figure S2 Diagnostic accuracy of the diagnostic algorithm from the NICE guideline

Number in black = number of patients at this step. Number in red = number of patients with doctor diagnosed asthma at this step. Algorithm + = diagnose asthma or suspect asthma. Algorithm - = refer for specialist assessment or consider alternative diagnosis. FEV1 = forced expiratory volume in 1 second. FVC = forced vital capacity. BDR = bronchodilator reversibility. FeNO = fractional exhaled nitric oxide. PEF = peak expiratory flow.

*362 patients would need 2 weeks PEF monitoring.

10.8 Co-author publication: Standardized reporting of wheezing illnesses in children – findings from the Swiss Paediatric Airway Cohort (SPAC).

De Jong CCM, **Pedersen ESL**, Ardura-Garcia C, Mueller-Suter D, Jochmann A, Singer F, Casaulta CA, Regamey N, Barben J, Moeller A, Goutaki M, Kuehni CE.

Original article

Own contribution: Help collect and enter data, help with conceptualization of study, help with data interpretation, revise manuscript.

Standardized reporting of obstructive airway disease in children – a national Delphi process

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Disclosure statement

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Abstract (244/250)

Background

Obstructive airway disease in children is heterogeneous, and there has been much discussion about phenotypes. This has resulted in heterogeneous diagnostic labelling in medical records.

Objective

To assess which words and aspects were used to describe a diagnosis of obstructive airway disease by Swiss paediatric pulmonologists, and to agree on a common way for future use.

Methods

We included letters from paediatric pulmonologists to referring physicians of children diagnosed with obstructive airway disease included in the Swiss Paediatric Airway Cohort. We assessed how diagnosis was described using thematic analysis (qualitative) to identify and group words with common content and descriptive analysis (quantitative) to assess the frequency of use. We performed a Delphi process to achieve a consensus on the aspects, which should be used in a standardised report of obstructive airway disease.

Results

Physicians used 123 unique words to describe obstructive airway disease. These words could be grouped into aspects and traits. The spectrum and frequency of traits varied by age, type of visit (first or follow-up), and by centre. We propose to use ... to describe obstructive airway disease in children aged 0-17 years, based on a consensus among specialists. (info will be added after delphi finished)

Conclusion

We found much heterogeneity in reporting of diagnosis, reflecting uncertainty in the diagnosis, and its subgroups (phenotypes). In the absence of an agreement on phenotypes,

we recommend a standardised reporting, which describes the aspects and traits that are relevant for treatment and follow-up.

1. What is already known about this topic?

Obstructive airway disease in children is heterogeneous, and there has been much discussion about phenotypes. This has resulted in heterogeneous diagnostic labelling in medical records. (25/35 words)

2. What does this article add to our knowledge?

This is the first study analysing how obstructive airway disease was described in letters from paediatric pulmonologists to referring physicians and propose a standardised way for future reporting based on a consensus among specialists (34/35 words)

3. How does this study impact current management guidelines?

In the absence of an agreement on phenotypes, we recommend a standardised reporting, which describes the aspects and traits that are relevant for treatment and follow-up. (24/35 words)

Word count: 2416/3500

Tables and figures: 4 tables, 4 figures/8

Supplementary material: 1 table, Delphi questionnaires

Keywords:

Asthma; Wheeze; Obstructive airway disease; Standardized reporting; Medical records; Traits

List of abbreviations

ICD – international classification of diseases

SPAC – Swiss Paediatric Airway Cohort

Introduction

Diagnosing obstructive airway diseases in children (wheezing illness, asthma) is difficult because symptoms vary over time and a stand-alone diagnostic test is lacking [1, 2]. Therefore, diagnosis always has a level of uncertainty. It is also heterogeneous and subtypes (phenotypes) or treatable traits of obstructive airway disease should be distinguished, but there is no agreement on how [3-6]. This uncertainty is reflected in the wording used by physicians to describe this diagnosis in medical records. Some physicians only report diagnosis as asthma, but most describe additional aspects such as severity, triggers or symptom control. Data from medical record are frequently used in research to ascertain past and present diagnoses. While medical records may be less vulnerable to recall bias and more objective than patient-reported data, use of diagnosis from medical records is complicated by heterogeneous reporting. This affects research based on this information sources for instance checking inclusion/exclusion criteria for observational or interventional research. Standardised reporting of obstructive airway disease would facilitate clinical research. It would also improve communication between doctors for clinical purposes, when a patient switches doctor or hospital.

A consensus among physicians on how to report obstructive airway disease in medical records is lacking. To overcome heterogeneous reporting the international classification of diseases (ICD) was developed. ICD-10 only differentiates allergic, non-allergic, mixed and not further specified asthma [7]. Most studies assess which aspects and traits are reported in guidelines and literature to describe obstructive airway disese [8-11]. Others tested algorithms to automate chart review in a primary care setting or assessed differences

between self-reported and medical records [12, 13]. It is not clear which aspects and traits paediatric pulmonologists list to describe obstructive airway disease in medical records. We aimed to (1) find out which words, aspects and traits were used by specialists (paediatric pulmonologists) to describe obstructive airway disease and based on this, (2) agree on a standard way of reporting obstructive airway disease, which describes the aspects and traits that are relevant for treatment and follow-up.

Methods

Study population and study design

We analysed the description of a diagnosis of obstructive airway disease in hospital letters from paediatric pulmonologists sent to the referring physicians (paediatricians or general practitioners). For this, we used the hospital letters collected at the baseline examination of the Swiss Paediatric Airway Cohort (SPAC). Details of this study have been published [14]. SPAC is an observational study including all children referred to paediatric pulmonary outpatient clinics for respiratory symptoms such as wheeze, cough, dyspnoe, or exercise related respiratory symptoms. For this study, we included children aged 0-17 years, who visited outpatient clinics between July 2017 and November 2018, and were diagnosed with an obstructive airway disease (Figure 1). Letters/records were included if the diagnosis list contained one of the following words: “Asthma”, “Wheeze”, or “Obstructive airway disease” (e.g. obstructive bronchitis). We excluded letters if the diagnosis list mentioned a fixed airway obstruction and letters from children for whom we did not receive a questionnaire. The study was approved by the Bernese ethics committee (KEB 2016-02176) and all participating parents and adolescents aged above 14 years gave informed consent.

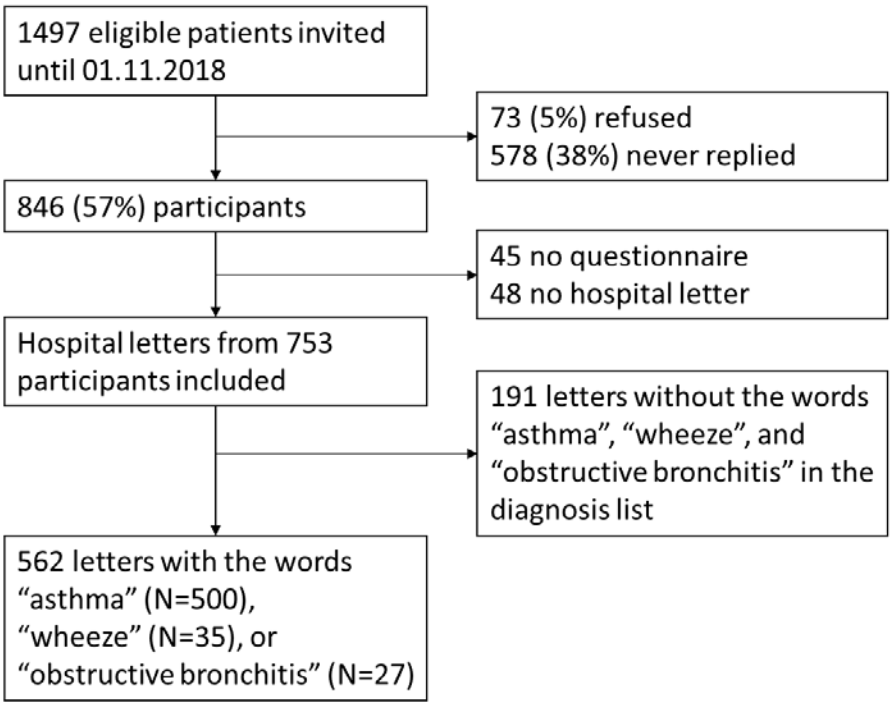

Figure 1: Flow chart of the study population

Study procedures

The paediatric pulmonologist wrote or supervised writing of the hospital letter to the primary care physician summarizing the findings, diagnoses, and procedures, at the end of the visit. All German speaking paediatric pulmonology outpatient clinics are board qualified training centres and lead by paediatric pulmonologists who passed the HERMES exam of the European Respiratory Society. Each month, we collected the hospital letters from all seven paediatric respiratory pulmonology outpatient clinics in the German speaking part of Switzerland. We entered the text from the diagnosis list in the REDCap database. The demographics and text was then exported to Nvivo version 12, to perform the qualitative analysis.

Qualitative analysis

To identify words used to describe obstructive airway disease and to group words with common content into aspects or traits, we used thematic analysis. We first identified and dropped the letters of which the diagnosis list did not contain the word ”Asthma”, ”Wheeze” or ”Obstructive airway disease” (figure 1). From the remaining letters, we identified each word used to describe obstructive airway disease in the diagnosis list (figure 2). Looking at the list of identified words, we grouped the words with common content into traits and other aspects (table 2).

Quantitative analysis

To display the frequency of traits and other aspects used to describe obstructive airway disease in children and stratify the results per age group, type of visit, and centre, we exported to STATA (for tables) and R (for graphs).

We defined three age groups: 0-4, 5-9 and 10-17 years based on the inability to perform lung function tests below the age of five and the increased self-management during the teenage years.

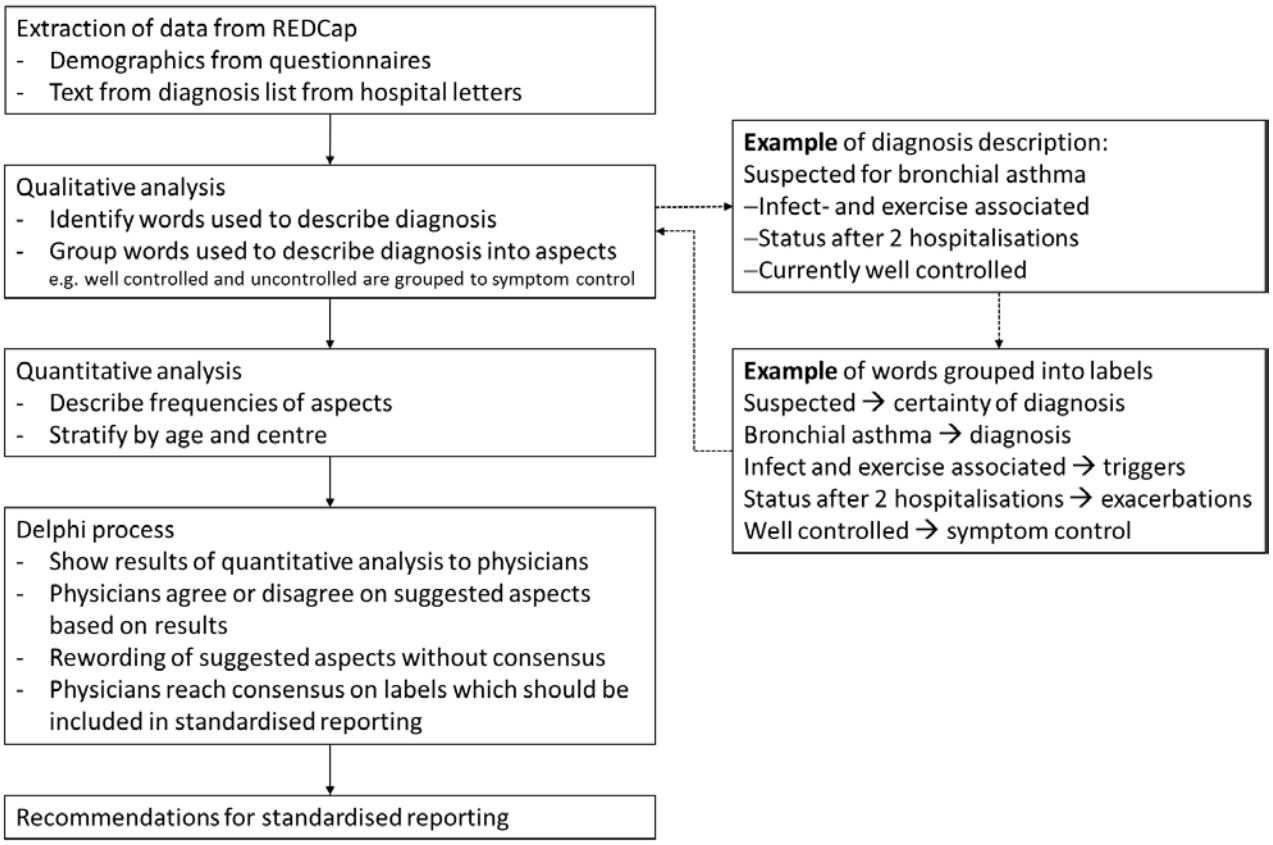

Figure 2: Flow chart of the analysis steps

Delphi process

To propose standardised reporting based on a Delphi process among paediatric pulmonologists, we developed several Delphi questionnaires (ongoing) [15]. The first Delphi questionnaire consisted of five groups of proposed recommendations based on our analysis. First, the aspects which should be used to describe obstructive airway disease in children. Second, the aspects which should not be stated in the diagnosis list, but may be stated somewhere else in the letter. Third, the grouping of aspects. Fourth, the order in which the aspects should be used, and fifth, additional considerations. The paediatric pulmonologists stated for each recommendation if they agreed or not and whether they had comments or suggestions. We analysed the level of agreement and developed a second Delphi questionnaire. This process was repeated until a consensus on all recommendations with an agreement of at least 70% was reached.

Statistical analysis

To visualise the spectrum of aspects given to children with obstructive airway disease, we plotted the relative frequencies of aspects in a Venn Euler diagram using the Venneuler package in R stratified by diagnosis (asthma or wheeze/obstructive bronchitis). To describe the frequency of aspects given to children with obstructive airway disease and compare aspects between age-groups, first or follow-up visit and clinics, we displayed proportions.

Results

Characteristics of the study population

We used hospital letters from 562 children. 1497 had been invited for SPAC by November 2018, of whom 846 (57%) participated and 562 (66%) were diagnosed with obstructive airway disease and had available information from the questionnaire and hospital letter (Figure 1). Of the 562 included children, 65% were male and the median age was 8 years (interquartile range (IQR) 5-11) (table 1). Most of the children reported wheeze (69%) and exercise related breathing problems (61%). Of the 562 participants, 509 (91%) used inhalation medication and 390 (69%) used inhaled corticosteroids.

Spectrum of words and aspects used to describe obstructive airway disease

In 500 (89%) children the diagnosis list contained the word asthma, in 35 (6%) ”wheeze” but not ”asthma”, and in 27 (5%) ”obstructive bronchitis” but not ”asthma” or ”wheeze”. We identified 123 unique words used to describe obstructive airway disease. These words were grouped into aspects (table 2). The aspects certainty of diagnosis, age and recurrence were usually mentioned in the beginning, while the traits therapy, symptom control and adherence were rather mentioned at the end of the diagnosis list.

Frequency of traits used to describe obstructive airway disease

Figure 3 represents the frequency of the most used traits used. In the 500 children with the diagnosis ”asthma”, the most frequently mentioned traits were test results (87%), triggers (85%), symptom control (27%), and certainty of diagnosis (23%). The test result mostly mentioned in the diagnosis list was the allergy test result (81%), other test results were only mentioned in a third of the patients. In the 62 children with the diagnosis ”wheeze” or ”obstructive bronchitis”, the most frequently mentioned traits were recurrence(chronic/episodic) (89%), test results (85%), triggers (71%), and exacerbations (23%). Test results most reported were allergy test results (45%).

Spectrum and frequency of traits used to describe obstructive airway disease by age

Table 3 shows differences by age in the spectrum and frequency of traits used to describe obstructive airway disease. Certainty of diagnosis, age, episodic, recurrent, diagnosis of wheeze/obstructive bronchitis, exacerbations, and predictive indices were reported more frequently in younger children. Chronicity, diagnosis of asthma, and symptom perception were increasingly reported with older age. Triggers, allergy test results, and symptom control were reported less frequently in children aged 0-4 years compared to children aged 5-17 years.

Spectrum and frequency of traits used to describe obstructive airway disease by visit and centre

Certainty of diagnosis, age, recurrence and the diagnosis wheeze/obstructive bronchitis were reported more frequently in hospital letters after a first visit than after a follow-up

visit (table 4). Seasonality, asthma, symptom perception, and diagnostic test results were reported more frequently in hospital letters after a follow-up visit than after a first visit. Table S1 shows differences among clinics. The traits mentioned in all centres were: certainty of diagnosis, age, recurrence, triggers, diagnosis of asthma, diagnosis of wheeze/obstructive bronchitis, exacerbations, diagnostic tests, and symptom control.

Recommended standardised reporting for obstructive airway disease based on the Delphi process

Figure 4 shows the cecommended standardised reporting for obstructive airway disease. We reached agreement of xx-xx% on the recommendations for standardised reporting of obstructive airway disease based after xx Delphi rounds. The delphi questionnaires used to come to an agreement can be found in the supplementary material. We reached an agreement of xx-xx% among physicians in the first round, xx-xx% in the second round and xx-xx% in the xx and final round. **(ongoing, I will add more info when delphi is finished)**

Discussion

This multicentre clinical study found that the spectrum of words, aspects and traits used to describe obstructive airway disease was wide. The 123 words used by paediatric pulmonologists could be grouped into aspects and traits using thematic analysis. The spectrum and frequency of aspects and traits varied by age, type of visit (first or follow-up), and by centre.

Comparison with other studies

This is the first study assessing the spectrum of words, aspects and traits used in medical records to describe the diagnosis of children with obstructive airway disease. Four studies have assessed which aspects and traits physicians should report in a standardised form to monitor asthma in primary care. A Swiss study performed a systematic review of scientific articles and clinical guidelines to identify evidence-based indicators (aspects and traits) which could be used to monitor chronic conditions in primary care [8]. They found 21 items for asthma. These items can be summarised in the following aspects and traits: diagnostic tests and/or results (spirometry, bronchial provocation test), symptoms, activity limitations, symptom control, smoking (habit and cessation advice), therapy, triggers, exacerbations, adherence. We found similar aspects and traits, except for smoking which is probably due to the younger age of our population. A Canadian study performed a literature review to identify a standardised asthma data set, but did not find any studies [16]. Therefore, they set up a team of health care workers, information management/technology experts, and health care administrators to select asthma data elements (aspects and traits). They selected the following aspects and traits for the first visit: certainty of diagnosis, diagnostic

tests and/or results (spirometry, bronchial provocation, and allergy test), exacerbations, smoking, occupation, triggers, preventive measures (environmental), adherence. For follow-up, they selected the following aspects and traits: asthma control, symptoms, exacerbations, activity limitations, diagnostic tests and/or results (spirometry), preventive measures (environmental, smoking cessation, immunisation), and therapy. We also found that physicians report certainty of diagnosis rather after the first visit than after a follow-up visit. Asthma control was not reported more often after a follow-up visit compared to a first visit. A Dutch study identified 65 items in guidelines to describe diagnosis of asthma [10]. They performed a Delphi process to achieve a consensus on the items, which should be included in electronic patient records suitable for general practice. They found that a modified Delphi procedure is an applicable method for determining the content of a registration protocol for an electronic case record. A starting point, such as a set of pre-existing guidelines is essential. This was in line with findings from our study. A study from the UK used a Delphi process to reach consensus on a minimal dataset for an international severe asthma registry [11]. The international team of 27 experts in the field of severe asthma research selected aspects and traits from existing national severe asthma registries. They reached consensus on the following categories: inclusion criteria (severity), occupation, medical history, comorbidity, diagnostic tests and/or results, asthma control, therapy, adherence and management plan. We found similar aspects and traits, except for occupation, comorbidity and management plan, which is probably due to the difference in age and severity.

Diagnostic labelling of obstructive airway disease has been a matter of debate. While many studies focus on defining phenotypes, some suggest to leave the phenotypes and rather

focus on traits which can be treated, because phenotypes are unstable over time, especially in children [3-6, 17, 18]. This study showed that for paediatric pulmonologists stating a diagnostic label or phenotype only was insufficient, because they stated various aspects such as traits which can be treated.

Strengths and limitations

Our study is the first to propose standardised reporting of diagnosis in children with obstructive airway disease. The proposal was based on an empirical study in a real-life clinical setting combined with a Delphi process among paediatric pulmonologists, which has never been done before. This method will facilitate successful implementation in clinics, because it is from paediatric pulmonologists for paediatric pulmonologists and based on real-life data. We could include over 500 children of all ages and from all centres in the German speaking part of Switzerland, which ensured the inclusion of a representative spectrum of aspects in the Delphi process. We did not include letters from hospitals in the French or Italian speaking part of Switzerland, because of language issues. We could not include all letters, because we were limited to participants in SPAC. We believe that this will not have introduced bias, as participation depended on parents and not on the reporting paediatric pulmonologists.

Implication in the clinic and future research

Standardised reporting of diagnosis and there aspects or traits are essential for using routinely collected data for research [19]. Physicians need to record detailed health data in every day care. However, if the recording is heterogeneous it is difficult to use it directly for research. Physicians or researchers then need to collect health data for research separately.

If the quality of recording improves and harmonises, physicians do not need to do double work for research [20]. Research could be done at a faster rate at lower cost and with larger sample sizes. This would enhance improvement of patient care.

Conclusion

We found much heterogeneity in reporting of diagnosis, reflecting uncertainty in the diagnosis, and its subgroups (phenotypes). In the absence of an agreement on phenotypes, we recommend a standardised reporting, which describes the aspects and traits that are relevant for treatment and follow-up.

Ethics approval and consent to participate

The Bernese ethics committee (KEB 2016-02176) approved the Swiss Paediatric Airway Cohort and all participating parents and adolescents aged above 14 years gave informed consent.

Authors' contributions

CdJ, EP, CAG, MG, and CK developed the concept and designed the study. CdJ, EP, DMS, AJ, FS, CC, NR, JB, and AM collected the data. CdJ analysed the data, with aid of EP, CAG, and MG. CdJ, EP, CAG, MG, and CK drafted the manuscript. All authors contributed to iterations and approved the final version.

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Availability of data and material

The SPAC dataset is available on reasonable request by contacting Claudia Kuehni.

Figure legends (each figure legend should be held to 60 words or less)

Figure 1 Flow chart showing the study population

Figure 2 Flow chart showing the study steps

Figure 3 Frequency of aspects and traits used in children

Figure 4 Recommended standardised reporting for obstructive airway disease based on Delphi process

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401

Table 1: Patient characteristics (N=562)

	Total n (%)	
Age		
0-4 years	112	(20)
5-9 years	211	(38)
10-17 years	239	(43)
Sex, male	365	(65)
Clinic		
A	187	(33)
B	149	(27)
C	80	(14)
D	66	(12)
E	35	(6)
F	25	(4)
G	20	(4)
First visit	226	(40)
Follow-up visit	336	(60)
Respiratory symptoms*		
Cough more than 4 weeks	169	(30)
Night cough	232	(41)
Exercise related breathing problems	343	(61)
Any wheeze	388	(69)
Dyspnoea	278	(49)
Inhalation medication*		
Any	509	(91)
SABA alone	119	(21)
ICS +/- SABA	203	(36)
ICS + LABA	187	(33)

* in the last 12 months

Table 2: The grouping of all wording into aspects or traits and the order of use (from top to bottom)

Aspects and traits	All words used
Disease label	Asthma Asthma bronchiale Small airways disease Episodic viral wheeze Multiple trigger wheeze Obstruktive bronchitis
Certainty of diagnosis	Verdacht auf Hochgradiger Verdacht auf Dringender Verdacht auf Möglicherweise Wahrscheinlich Sehr wahrscheinlich Exclusion of differential diagnosis Schweisstest Bronchoskopie Chest X-ray CT-Thorax
Age-related phenotype	Frükindliches Kleinkindes Infantiles
Symptoms	Husten Wheeze Atemnot / ohne Atemnot Asymptomatisch
Symptom perception	Subjektiv Slechter perzeption
Pattern of symptoms over time	Rezidivierende Wiederholte Mehrfacher Frequenz
Factors leading to symptoms	Allergisch Exogen Pollinosum Nicht allergisch Infekt Anstrengung Multifaktoriell Wetter Psychisch Triggers unklar
Related measures of disease severity	Leichtes/Mildes Difficult to treat **Exacerbations** Exazerbation Hospitalisation Atemunterstützung Intensivmedizin Respiratorische partiallinsuffizienz **Stability** Instabil Stabil/Sehr stabil Brittle **Effect on daily life** Leistungsintoleranz Keine Einschränkungen

Aspects and traits	All words used
Lung function	Lungenfunktion -Obstruktiv -Leichte -Mittelschwere -Nicht obstruktiv -Gemischt obstruktiv und restriktiv FEV1 Bronchodilator Reversibilität -Teilreversibilität/Vollständig/Fixiert
Airway inflammation	FeNO
Airway hyper-responsiveness	Belastungs-lungenfunktion Methacholine Mannitol Bronchiale Hyperreagibilität -Leichte/Mittelschwere/Schwere -Keine
Atopy	Sensibilisierung -Klinischer Relevanz/ -Fraglicher -Gesicherter -Wenig -Eindeutig -Hochrelevant -Wahrscheinlich -Wahrscheinlich nicht -Ohne eindeutige/Keine
Therapy	SABA, Ventolin LABA ICS, Axotide Flutiform, Seretide, Symbicort LTRA Montelukast Bronchovaxom Omalizumab Ohne Therapie
Symptom control	Kontrolliert Kontrolliert nach GINA Gut kontrolliert Vernünftig kontrolliert Partiell bis gut kontrolliert Partiell kontrolliert Teilweise kontrolliert Mässig kontrolliert Ungenügend kontrolliert Unkontrolliert Nicht kontrolliert Ungenügend eingestellt Slecht eingestellt Mässiger Kontrolle Nicht genügend Kontrolle Unzureichender Symptomkontrolle
Compliance	Malcompliance Mässige compliance Oft vergessen

* Words used directly as trait without grouping were not listed in this table: chronic/episodic, since, seasonal/perennial, therapy response and asthma predictive index(API)/predicting asthma risk in children(PARC).

I will adjust the following two tables, once table 2 has been finalised.

Table 3: The frequency of aspects and traits given to children with wheezing illnesses at paediatric respiratory outpatient clinics stratified by age

Aspects and traits	**Total** N=562		**Age 0-4** N=112		**Age 5-9** N=211		**Age 10-17** N=239		**P-trend**
	n	(%)	n	(%)	n	(%)	n	(%)	
Certainty of diagnosis	117	(21)	32	(29)	48	(23)	37	(15)	0.003
Age	49	(9)	37	(33)	10	(5)	2	(1)	<0.001
Chronic	2	(<1)	0	(0)	0	(0)	2	(1)	0.148
Episodic	44	(8)	27	(24)	13	(6)	4	(2)	<0.001
Recurrent	69	(12)	51	(46)	17	(8)	1	(<1)	<0.001
Since	1	(<1)	0	(0)	1	(<1)	0	(0)	0.765
Seasonal	12	(2)	2	(2)	6	(3)	4	(2)	0.784
Perennial	7	(1)	0	(0)	3	(1)	4	(2)	0.225
Triggers	468	(83)	82	(73)	180	(85)	206	(86)	0.007
Asthma	500	(89)	57	(51)	204	(97)	239	(100)	<0.001
Wheeze/obstructive bronchitis	62	(11)	55	(49)	7	(3)	0	(0)	<0.001
Symptoms	38	(7)	12	(11)	9	(4)	17	(7)	0.427
Limitations	3	(1)	0	(0)	0	(0)	3	(1)	0.076
Symptom perception	11	(2)	0	(0)	3	(1)	8	(3)	0.027
Severity	16	(3)	0	(0)	7	(3)	9	(4)	0.072
Exacerbations	73	(13)	28	(26)	30	(14)	15	(6)	<0.001
Stability	7	(1)	1	(1)	4	(2)	2	(1)	0.770
Diagnostic tests	489	(87)	90	(80)	188	(89)	211	(88)	0.082
Allergy tests	431	(77)	62	(55)	175	(83)	194	(81)	<0.001
Therapy	46	(8)	8	(7)	18	(9)	20	(8)	0.745
Therapy response	3	(1)	2	(2)	0	(0)	1	(0)	0.200
Symptom control	139	(25)	8	(7)	64	(30)	67	(28)	<0.001
Compliance	3	(1)	0	(0)	0	(0)	3	(1)	0.076
Asthma Predictive Index (API) / Predicting asthma risk in children (PARC)	10	(2)	8	(7)	2	(1)	0	(0)	<0.001

*p-value calculated by using test for trend among ordered groups

Table 4: The frequency of aspects and traits given to children with wheezing illnesses at paediatric respiratory outpatient clinics stratified by first or follow-up visit

Aspects and traits	**First visit** N=226		**Follow-up** N=336		**P-value***
	n	(%)	n	(%)	
Certainty of diagnosis	64	(28)	53	(15)	<0.001
Age	31	(14)	18	(5)	0.001
Chronic	2	(1)	0	(0)	0.245
Episodic	21	(9)	23	(7)	0.290
Recurrent	38	(17)	31	(9)	0.007
Since	0	(0)	1	(<1)	0.412
Seasonal	1	(<1)	11	(3)	0.023
Perennial	3	(1)	4	(1)	0.886
Triggers	185	(82)	283	(84)	0.461
Asthma	193	(85)	307	(91)	0.027
Wheeze/obstructive bronchitis	33	(15)	29	(9)	0.027
Symptoms	10	(4)	28	(8)	0.070
Limitations	1	(<1)	2	(1)	0.807
Symptom perception	1	(<1)	10	(3)	0.033
Severity	8	(4)	8	(2)	0.418
Exacerbations	28	(12)	45	(13)	0.729
Stability	2	(1)	5	(1)	0.527
Diagnostic tests	187	(83)	302	(90)	0.014
Allergy tests	162	(72)	269	(80)	0.021
Therapy	15	(7)	31	(9)	0.272
Therapy response	2	(1)	1	(<1)	0.349
Symptom control	48	(21)	91	(27)	0.115
Compliance	0	(0)	3	(1)	0.154
Asthma Predictive Index (API) / Predicting asthma risk in children (PARC)	5	(2)	5	(1)	0.524

*p-value calculated by using chi-square test

Supplementary material (will be adapted once table 2 and the delphi process are finalised)

Table S1: The frequency of aspects and traits given to children with wheezing illnesses at paediatric respiratory outpatient clinics stratified by centre

Aspects and traits	**Clinic A**		**Clinic B**		**Clinic C**		**Clinic D**		**Clinic E**		**Clinic F**		**Clinic G**	
	N=187		N=149		N=80		N=66		N=35		N=25		N=20	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Certainty of diagnosis	30	(16)	44	(30)	24	(30)	6	(9)	5	(14)	6	(24)	2	(10)
Age	16	(9)	18	(12)	3	(4)	5	(8)	3	(9)	4	(16)	0	(0)
Chronic	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	2	(10)
Episodic	20	(11)	8	(5)	9	(11)	3	(5)	0	(0)	2	(8)	2	(10)
Recurrent	17	(9)	25	(17)	11	(14)	5	(8)	6	(17)	1	(4)	4	(20)
Since	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)	1	(5)
Seasonal	3	(2)	1	(1)	2	(3)	0	(0)	1	(3)	1	(4)	4	(20)
Perennial	0	(0)	0	(0)	3	(4)	0	(0)	0	(0)	2	(8)	2	(10)
Triggers	140	(75)	136	(91)	73	(91)	60	(91)	30	(86)	18	(72)	11	(55)
Asthma	169	(90)	130	(87)	67	(84)	65	(98)	31	(89)	24	(96)	14	(70)
Wheeze/obstructive bronchitis	18	(10)	19	(13)	13	(16)	1	(2)	4	(11)	1	(4)	6	(30)
Symptoms	8	(4)	11	(7)	9	(11)	0	(0)	0	(0)	0	(0)	10	(50)
Limitations	1	(1)	0	(0)	1	(1)	0	(0)	0	(0)	0	(0)	1	(5)
Symptom perception	3	(2)	0	(0)	3	(4)	3	(5)	0	(0)	0	(0)	2	(10)
Severity	4	(2)	8	(5)	0	(0)	0	(0)	1	(3)	0	(0)	3	(15)
Exacerbations	19	(10)	22	(15)	17	(21)	10	(15)	2	(6)	2	(8)	1	(5)
Stability	0	(0)	2	(1)	4	(5)	0	(0)	1	(3)	0	(0)	0	(0)
Diagnostic tests	140	(75)	141	(95)	80	(100)	64	(97)	21	(84)	27	(77)	16	(80)
Allergy tests	124	(66)	128	(86)	74	(93)	60	(91)	21	(84)	22	(63)	2	(10)
Therapy	4	(2)	11	(7)	17	(21)	3	(5)	6	(17)	0	(0)	5	(25)
Therapy response	1	(1)	1	(1)	0	(0)	0	(0)	0	(0)	0	(0)	1	(5)
Symptom control	38	(20)	49	(33)	27	(34)	7	(11)	4	(11)	12	(48)	2	(10)
Compliance	1	(1)	0	(0)	0	(0)	1	(2)	0	(0)	0	(0)	1	(5)
API/PARC*	5	(3)	4	(3)	0	(0)	0	(0)	0	(0)	1	(4)	0	(0)

* Asthma Predictive Index (API) / Predicting asthma risk in children (PARC)

10.9 Co-author publication: Paediatric cohort studies on lower respiratory diseases and their reporting quality: a systematic review

Ardura-Garcia C, Mozun R, **Pedersen ESL**, Otth M, Mallet MC, Goutaiki M, Kuehni CE

Systematic review

Own contribution: Conceptualization of study, literature research, abstract and full-text screening of articles.

Paediatric cohort studies on lower respiratory diseases and their reporting quality: a systematic review

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Take home message: We need a joined effort of editors, reviewers and authors to improve the reporting quality of paediatric cohort studies for respiratory problems.

Conflict of interest: None

Authors contributions: Claudia E Kuehni, Myrofora Goutaki, Cristina Ardura-Garcia, Eva Pedersen, and Rebeca Mozun conceptualised and designed the study. Cristina Ardura-Garcia, Rebeca Mozun, Eva SL Pedersen, Maria Otth, and Christina Mallet performed the screening and data extraction. Cristina Ardura-Garcia analysed the data and drafted the manuscript. All authors critically revised the manuscript and approved the final manuscript as submitted.

Key words: systematic review, paediatric, cohort studies, respiratory symptoms

Abstract

The paediatric respiratory research community uses cohort studies extensively. However, the landscape of these studies and their quality of reporting has not been assessed.

We performed a systematic review of publications on cohort studies reporting on paediatric lower respiratory problems published in 2018. We searched Medline and EMBASE and extracted data on the studies' and journals' characteristics. We assessed the number of items of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist that a random sample (100 papers) reported. We analysed factors associated with the STROBE score and with the most poorly reported items, using multivariable Poisson and logistic regression

Of the 21 319 records identified, 369 full-text articles met our inclusion criteria. Most papers studied asthma aetiology through birth cohorts and were based in Europe or North America. The reporting quality was poor: 15% reported the 22 STROBE items; median score: 18 (IQR: 16-21). The most poorly reported items were: sources of bias, sample size, statistical methods, descriptive results and generalisability. None of the studies' or journals' factors were associated with the STROBE score.

We need a joined effort of editors, reviewers and authors to improve the reporting quality of paediatric cohort studies on respiratory problems.

Words: 200/200

Introduction

Cohort studies are extensively used in paediatric respiratory research to investigate risk factors, incidence and natural history of disease. The strengths of the longitudinal design include establishing temporality and reducing information bias. However, the study design has limitations, like high costs, selection bias, attrition bias, and residual confounding. There are solutions to overcome or mitigate these disadvantages like retrospective cohort design, nested case-control studies or linkage to nationwide available datasets. The use of these strategies, the type of questions investigated and the quality of reporting of cohort studies has not been assessed in paediatric respiratory research.

Adequate reporting is key for reproducibility of research and translation of results into clinical practice. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) is an international, multidisciplinary and collaborative initiative stated in 2004 to enhance the reporting quality and dissemination of observational studies [1]. The STROBE statement is being increasingly endorsed by journals, but mandatory submission of its checklist is not yet common practice for observational studies as it is for randomized controlled trials. Studies assessing the fulfilment of the STROBE criteria suggest that reporting quality is generally poor and that some items are frequently underreported [2-4]. Certain factors have been associated with reporting quality, such as jounal's impact factor and STROBE endorsement policy, the authors' affiliation, and publication type (peer reviewed or not) [3, 5-7]. Identifying which STROBE items are commonly misreported in paediatric respiratory cohort papers and which modifiable factors are associated with poor reporting may raise awareness and help improve the quality of publications in this area. We therefore conducted a systematic review of papers published in 2018 to present the landscape of cohort studies addressing paediatric lower respiratory problems, to describe the reporting quality of these papers according to STROBE guidelines and to examine characteristics associated with reporting quality.

Methods

The predefined review protocol that we followed for this systematic review has been registered in the Open Science Framework (OSF) repository (Registration DOI 10.17605/OSF.IO/F8X3B). We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, research checklist online) [8] to report our findings.

Eligibility criteria

We searched for papers reporting on lower respiratory problems from paediatric cohort studies worldwide, published in 2018 in peer-reviewed journals. For this we used all the following specific inclusion criteria: (1) cohort study design (exposure measured before outcome, with at least two time points with prospective data collection), including nested case-control studies; (2) children under 18 years of age at study baseline, or with separate results reported for children, or for rare diseases, if more than 50% of the study population were children; (3) lower respiratory problems and evaluations of lower respiratory health as outcomes (including respiratory symptoms, test results such as lung function, diagnosis and prognosis)or lower respiratory problems and evaluations of lower respiratory health as exposures (including respiratory symptoms, test results such as lung function, diagnosis, management and prognosis).

We excluded studies with any of the following criteria: (1) reports not in English, (2) published before 1st January 2018 or after 31st December 2018 (3) non-original papers (conference abstracts, editorials and reviews) (4) follow-up time <3 months (to exclude papers on short-term outcomes of hospitalised patients) and (5) studies with <50 participants to exclude small case series (for rare diseases where smaller sample sizes are expected we excluded if there were <20 participants).

Information sources and search strategy

We searched Medline and EMBASE from 1st January 2018 to 31st December 2018, on April 17th 2019. We used a reference management software (EndNote X8, Thomson Reuters) to import the records and remove duplicates. We provide the full search strategy in the online supplementary information.

Study selection

One reviewer screened titles and abstracts to assess eligibility according to the described criteria. In a second step, a single reviewer screened full-text papers of selected studies and recorded the reasons for exclusion in an Excel form.

Data extraction

We extracted data from the selected papers using a standardised pre-piloted data collection Excel form. We extracted information on the characteristics of the manuscript (author, journal, location and year of publication) and the study (cohort name and size, study design, type of research question, main diseases of interest, source of exposure and outcome data, use of longitudinal analysis, follow-up time and age at baseline). We did not include a risk of bias assessment, as the results were not extracted and evaluated.

Definitions

Journals were classified into thematic categories according to the InCites Journal Citation Report classification. If a journal appeared in two different categories, it was classified as the first in which it appeared in this order: respiratory, allergy, infectious diseases, public health/ epidemiology/ environment, paediatrics, general medicine and any other category (Supplementary Table 1). The diagnoses studied were grouped into: asthma or wheeze, respiratory infectious diseases, rare diseases (defined as occurring in fewer than 1 in 2000

people, and including bronchopulmonary dysplasia, diaphragmatic hernia, cystic fibrosis and primary ciliary dyskinesia), lung function in healthy children and other problems (including cough, respiratory distress syndrome, pneumothorax and unspecific respiratory symptoms).

Assessment of reporting quality

We selected a random sample of 25% (100) of the selected papers and assessed how close the manuscript followed the STROBE recommendations for the reporting of cohort studies. We used a standardised data collection Excel form and recorded the adherence to each of the 22 items present in the STROBE checklist for the reporting of cohort studies. We extracted information on factors with a plausible association to reporting quality and/or those previously reported in similar published studies. These included the impact factor and percentage ranking in the highest category of the journal where each manuscript was published, from the InCites Journal Citation Report. We also searched the journals' webpages to collect information on whether the journal belongs to a scientific society and on the reporting recommendations (classified into no recommendation (none), recommending to follow any reporting guideline, recommending to follow STROBE reporting guidelines and mandatory attachment of the STROBE checklist at the time of manuscript submission).

Synthesis of results and analysis

We summarised the results (absolute numbers and proportions) of the study characteristics, the journals where they were published and the reporting quality according to the STROBE statement using tables and graphs. We used Poisson regression to study univariable associations between the study's characteristics and the number of items from the STROBE checklist that were reported in the manuscript. We reported the rate ratio with 95% confidence interval, and the p value of the likelihood ratio test. We then applied logistic regression to study univariable associations between the study's characteristics and the reporting of the 4 items

from the STROBE checklist that were most poorly reported: item 9 (bias), item 12 (statistics), item 14 (descriptive results) and item 21 (generalisability). We reported the odds ratio with 95% confidence interval for each item separately. For both regression analyses, we included the factors described above.

Results

Of the 15 846 records identified through database searching, 890 were selected based on title and abstract and 369 full-text articles were finally included in the systematic review (Figure 1). Of the 521 full-text articles excluded, 77 were not a cohort study and 24 did not include a longitudinal analysis (e.g. used cross-sectional data from a cohort study).

Most studies were located in Europe (161, 44%) or North America (108, 29%), with few from other locations, especially Africa (17, 5%) and South America (12, 3%) (Figure 2). The median sample size was of 746 children (IQR 187-4535). Forty one percent of the studies had a birth or pregnancy cohort design, followed by prospective clinical cohorts (109, 30%) and non-birth population-based cohorts (56, 15%). Median follow-up time was 5 years (IQR: 1-10 years). A quarter (85, 23%) used linkage with routine datasets and there were very few nested case-control studies (7, 2%). The most frequent sources of exposure data were questionnaires/interviews (128, 35%) or direct examination/diagnostic tests (134, 36%), while outcomes were normally obtained from questionnaires/interviews (157, 43%).

The main diagnosis of interest in the included studies included was asthma or wheeze (214, 58%) and the main research questions related to aetiology (194, 53%) followed by natural history or prognosis (116, 31%). The research questions varied by diagnosis of interest (Figure 3a). Studies on asthma and lung function answered questions mostly on aetiology or risk

factors, while natural history and prognosis was more common in studies of rare diseases and other diagnoses. Disease phenotyping was mostly studied in papers on respiratory infectious diseases or rare diseases. Similarly, sample size of the study population also varied by diagnosis of interest (Figure 3b). More than half of the studies on asthma had more than 1000 participants, while 40% of those on rare diseases had less than 100 participants.

The included cohort studies were mostly published in respiratory (103, 28%) or allergy/immunology journals (88, 24%) (Figure 2). Of the individual journals, those with 10 or more papers were either highly specific (Paediatric pulmonology, Paediatric Allergy& Immunology and Journal of Asthma) or high impact respiratory journals (Journal of Allergy and Clinical Immunology, Thorax and European Respiratory Journal). There was only one general journal (PlosONE) (data not shown). There were some differences in the study design, sample size and research question between journals, though the largest differences were observed in the diagnosis of interest (Supplementary Table 2). Papers on asthma were published mainly in allergy/immunology or respiratory journals and those on respiratory infectious diseases in their respective journals. Papers on other diagnoses were more evenly distributed, with the exception of the allergy/immunology journals that published almost exclusively on asthma.

The reporting quality of the papers was relatively poor (Table 1). Only three (8%) of the 369 included papers mentioned the STROBE statement in the text. Of the 100 subsampled publications, only 15% included all the 22 items mentioned in the STROBE checklist. The median number of elements missing from the checklist was 4 (IQR 1-6). The most frequently missed items were a correct description of the efforts to address potential sources of bias (item 9, missing in 42%), the study size explanation (item 10, missing in 36%), description of the statistical methods (item 12, missing in 62%), of the study participants' characteristics (item 14, missing in 44%), and the discussion of the generalisability of the study findings (item 21, missing

in 49%). For the reporting of statistical methods and the descriptive data of the study participants (items 12 and 14), one frequent flaw was the lack of description of the number of participants with missing data for each variable (item 14b, missing in 41%) and the explanation of how the missing data were addressed (item 12c, missing in 57%).

Table 2 shows the results of the univariable Poisson regression analysis of the factors associated with the number of reported items from the STROBE checklist for cohort studies. None of the studied factors was clearly associated with the STROBE score. The journal's characteristics (belonging to a society, impact factor, percentage ranking and journal category), continent of study and main diagnosis of interest were not associated with the STROBE score. Only studies on treatment effects had a lower score (poorer reporting) when compared to those with an aetiological research question (IRR 0.8, 95% CI 0.7-0.97). Table 3 shows the association between these same characteristics and the reporting of 4 specific items (those that had been reported in less than 60% of the manuscripts). As previously, most tested factors were not associated with the reporting of any of the 4 specific items, except for the location of the study, showing a smaller odds to report these items if the study was undertaken in Africa, Asia or the Pacific, compared to Europe. The study of treatment effects or of natural history of disease/prognosis vs. aetiology, had also a lower odds of reporting 3 of the items. As for the journal reporting recommendations, manuscripts published in journals that recommended following any reporting guideline were more likely to discuss the generalisability of the study findings compared to those published in journals with no recommendations.

Discussion

Summary of main findings

This systematic review found that reporting quality of cohort studies on paediatric lower respiratory problems was poor; only 15% of the manuscripts included all the recommended

items from the STROBE checklist and 42-63% missed specific items such as a correct description of statistical methods**.** Most published paediatric cohort studies were based in Europe and North America, answering research questions on aetiology and risk factors, and centred on asthma or wheeze. The most frequently used design were birth cohorts with only limited use of alternative strategies that may reduce the costs of cohort studies, such as record linkage or nested case-control studies. Finally, most studies were published in specialised respiratory or allergy journals.

Interpretation of results

During the screening process, we found that one fifth (101) of the 521 excluded full-text papers were actually not cohort studies (77) or did not use a longitudinal analysis (24), despite appearing in a search using specific search terms such as “cohort” or “follow-up”, and although we had already excluded papers based on the information in the title or abstract. This was sometimes due to the incorrect use of the word “cohort” and the absence of a clear description of the study design in the abstract or title. This information was still missing in 17% of the included manuscripts. The cohort studies on paediatric lower respiratory problems in 2018 that we analysed, focused mostly on aetiology of asthma and were based in Europe or North America. Lower respiratory infectious diseases, such as pneumonia or tuberculosis, which are a major cause of death in children under 5 years of age worldwide [9], were the focus of only 15% of the studies. This may be because most of the studies are based in high income countries, whereas the burden of respiratory infectious diseases is much higher in low and middle-income countries [9]. The most commonly used design was the birth or pregnancy cohort study. This is an excellent design to study early life factors and their influence on disease, but also quite expensive as it needs a very large sample size to achieve an adequate number of children with a specific disease and a long follow-up. Cheaper and quicker designs such as nested case-control studies or retrospective chart reviews were rarely used (3% and 9%, respectively). Linkage with

routine data is an efficient strategy to reduce follow-up time and obtain large sample sizes at a low cost (even whole population studies) (Lodge 2018). This strategy was used only in one quarter (85) of the included studies, and limited to countries with adequate electronic record keeping and unique personal identifiers (such as the social security number) that enables linkage between different datasets.

Even though reporting quality of observational studies improved after the publication of the STROBE statement [6], current studies in different medical fields have continued to find poor or at most moderate adherence to STROBE reporting criteria [2-7, 10-14], similar to our study. The items we identified as being frequently missed, such as the description of statistical methods, the sample size estimation or the potential sources of bias have been also reported in previous studies [3, 6, 7, 10, 11, 13, 14]. These items are essential to enable other researchers to reproduce the study and to evaluate its internal and external validity. Missing data and loss to follow up are common limitations of cohort studies, but the implementation of specific statistical strategies may attenuate its impact. The handling of missing information was poorly reported in the papers included in this review, both in the methods (43% of papers) and results (59%) section, resulting in a possible source of bias. A plausible reason for not reporting all the STROBE items may be the limitation of manuscript's length, reducing the amount of information that may be included in the paper. However, most journals offer the possibility of including supplementary online text and tables, enabling the authors to report as much detail as necessary. On the other hand, authors may not be aware of the existence of the STROBE statement [15] or they may deliberately omit certain information such as missing data to increase the publication chances. In this case, it is the journals' responsibility to inform the authors about the different reporting guidelines for each study design. Cohort studies may need to also adhere to other reporting guidelines depending on the aim of the manuscript, such as the TRIPOD (Transparent reporting of a multivariable prediction model for individual prognosis

or diagnosis)[16] or STARD (Standards for Reporting Diagnostic Accuracy)[17] statements for prognosis and diagnostic studies, or to specific STROBE extensions, such as RECORD (REporting of studies Conducted using Observational Routinely-collected health Data)[18] or STREGA (STrengthening the REporting of Genetic Association Studies)[19]. These reporting guidelines are all listed in the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network homepage (https://www.equator-network.org/). Journals should promote adherence to reporting guidelines through a compulsory attachment of the reporting checklist at submission and as an online supplement for readers. In addition, journals should implement further measures such as involving reviewers in checking reporting quality or even employing a journal methodologist to check manuscripts substantially before final acceptance. Only by applying this measure in a strict way, as it is done with randomized controlled trials, will the reporting quality of observational studies improve and become standardised.

The poor quality of reporting was not associated with the characteristics of the journal in our study. It did not depend on the journal's impact factor, percentage ranking, society ownership, category (by subject), or reporting recommendations. Similarly, it was not associated with the study's location, research question or main diagnosis of interest, except for a decreased STROBE score of papers reporting on treatment effects compared to aetiology. Previous studies have found quality of reporting of observational studies to be associated with some of these factors, such as the journal's impact factor [7] and authors guidelines [6], the publication type (peer-reviewed vs report) [3, 5] or the author's affiliation (public health agency vs academic) [5]. However, these findings are not consistent [14] and are sometimes based on small samples (<80 manuscripts) in specific fields. This shows that reporting quality of cohort studies in paediatric respiratory research needs to be improved globally.

Strengths and limitations

This systematic review is the first to describe the characteristics of cohort studies reporting on paediatric lower respiratory problems published recently and to assess their reporting quality according to the STROBE statement. We collected detailed information on a large number of studies published worldwide. However, the review has some limitations. First, we did not extend our search to specific databases from South America, Africa or Asia and limited the included studies to those published in English. This may have been one of the reasons for the under-representation of these regions of the world. However, the most important and relevant studies are normally published in English and indexed in Medline or Embase to increase accessibility. Second, the large number of studies included precluded a duplicate screening and data extraction. However, we used well-defined criteria for manuscript inclusion and exclusion. Third, the criteria we used to evaluate the adherence to each of the STROBE checklist's items were not very strict. For example, when evaluating the information on confounders or reporting of limitations, we only evaluated if confounders were considered or if limitations were mentioned. We did not study in detail each manuscript to assess if the confounders included or the limitations described were correct and complete. Therefore, our evaluation of the reporting quality is quite optimistic and reporting quality may be even poorer.

Conclusion

The findings of this review may inform both researchers (authors) and journals (editors) on how to increase reporting quality of papers of cohort studies reporting on paediatric lower respiratory problems and what areas of research are neglected. Researchers should follow reporting guidelines (either STROBE or as appropriate) closely when submitting a manuscript and should check these when reviewing other researchers' manuscripts. More resources and expertise should be allocated to investigate on the neglected respiratory diseases all over the world. The use of nested case-control studies, well designed retrospective chart reviews and linkage of routine data with study data should be borne in mind when designing a cohort study

to reduce costs. On the other side, editors from international journals should encourage the publication of studies focused on lower respiratory infections and rare diseases, and those based in low and middle-income countries. Journals should not only endorse the STROBE statement for the reporting of cohort studies, but should demand authors to attach the STROBE checklist during the submission process and ask reviewers to report any missing item in the manuscript. Only through a joined effort of editors, reviewers and authors may we improve the poor reporting quality of paediatric cohort studies on respiratory problems.

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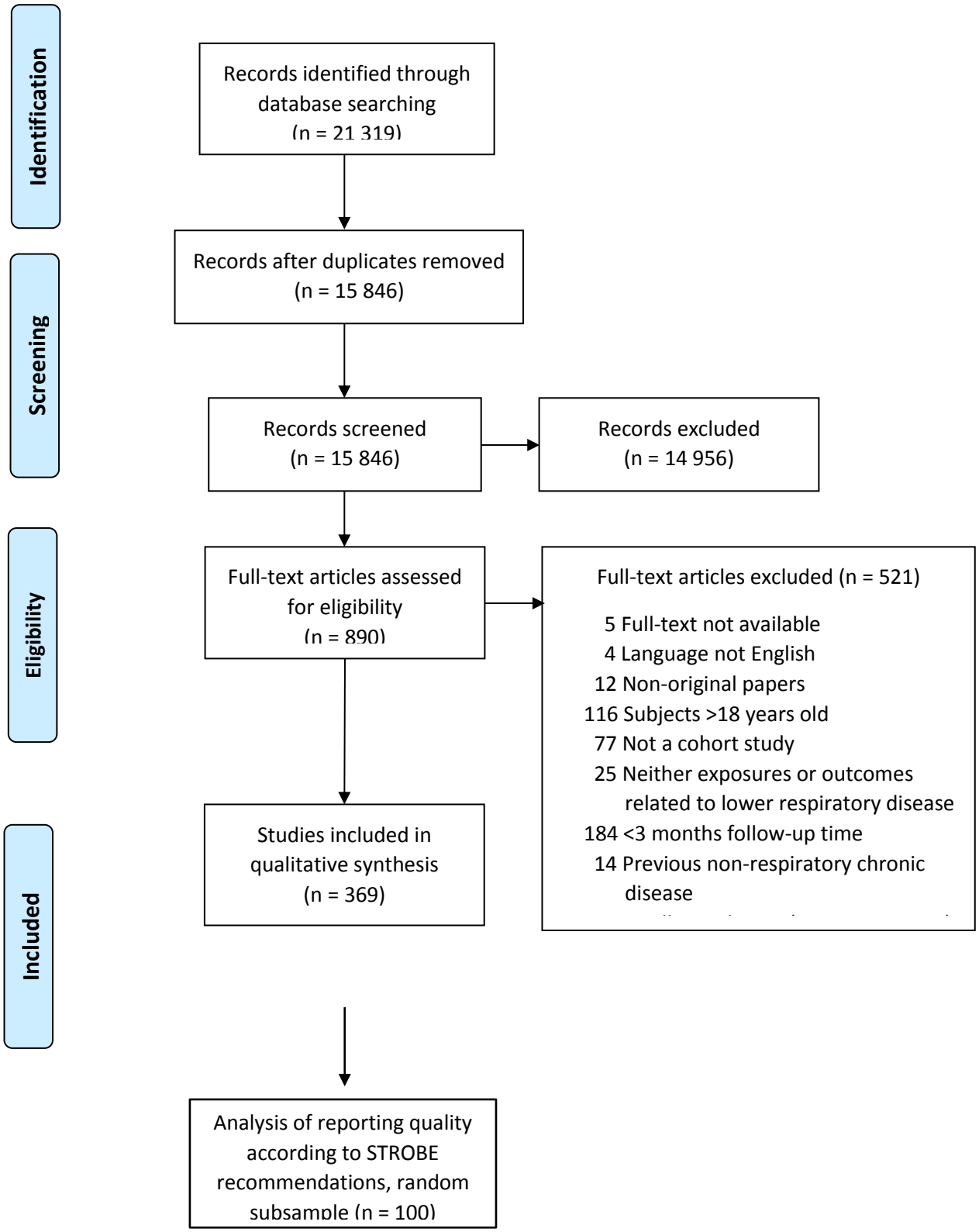


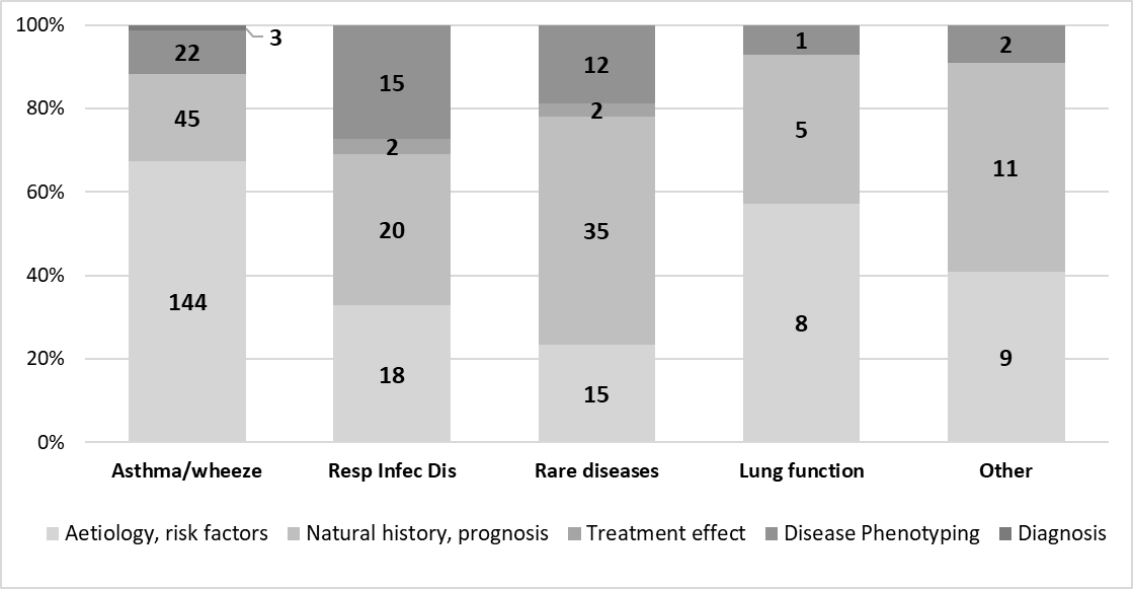
Figure 1: Flow diagram of included and excluded studies.

Table 1: Characteristics of cohort studies reporting on paediatric respiratory problems in 2018 (N= 369)

	N	Percentage
Location		
Europe	161	44
North America	108	29
Asia	37	10
Pacific	27	7
Africa	17	5
South America	12	3
Several continents	7	2
Sample size (median, IQR) (N= 367)	746 (187-4535)	
Sample size category (N= 367)		
<100	48	13
100 - 999	160	43
1 000 – 9 999	87	24
≥ 10 000	72	20
Study design		
Birth/pregnancy cohort	152	41
Clinical cohort (prospective)	109	30
Population-based cohort (after birth)	56	15
Retrospective chart review	35	9
RCT with continued follow-up	10	3
Nested case-control study	7	2
Linkage with routine data (N = 367)	85	23
Research question		
Aetiology/ risk factors / genetics	194	53
Natural history / prognosis / trajectories	116	31
Treatment effects	52	14
Diagnosis	4	1
Disease phenotyping	3	1
Main diagnosis of interest		
Asthma or wheeze	214	58
Rare diseases*	64	17
Respiratory infectious diseases	55	15
Lung function (healthy children)	14	4
Other diagnoses**	22	6
Source of baseline data (multiple possible)		
Questionnaire / interview	128	35
Direct examination /laboratory /diagnostic tests	134	36
Hospital record	91	25
Linkage of routine datasets	66	18
Treatment given	23	6
Source of outcome data (multiple possible)		
Questionnaire / interview	157	43
Direct examination /laboratory /diagnostic tests	83	22
Hospital record	66	18
Linkage of routine datasets	63	17
Follow-up time, years (median, IQR) (N= 360)	5 (1-10)	
Journal category[#] (multiple possible)		
Respiratory	103	28
Allergy / Immunology	88	24
Paediatrics	57	15
Pub health / epidemiology / environment	37	10
Infectious diseases	14	4
General Medicine	23	6
Other categories	47	13

*Rare diseases include: bronchopulmonary dysplasia, diaphragmatic hernia, cystic fibrosis and primary ciliary dyskinesia. **Other diagnoses include: cough, respiratory distress syndrome, pneumothorax and unspecific respiratory symptoms. #Categories according to the InCites Journal Citation Report, if a journal appeared in 2 categories, it was classified as the first in which it appears in this order: respiratory, allergy, infectious diseases, public health/epidemiology/environment, paediatrics, general medicine and any other category. IQR: inter-quartile range, RCT: randomized controlled trial.

A. Research question by diagnosis of interest



B. Sample size by diagnosis of interest

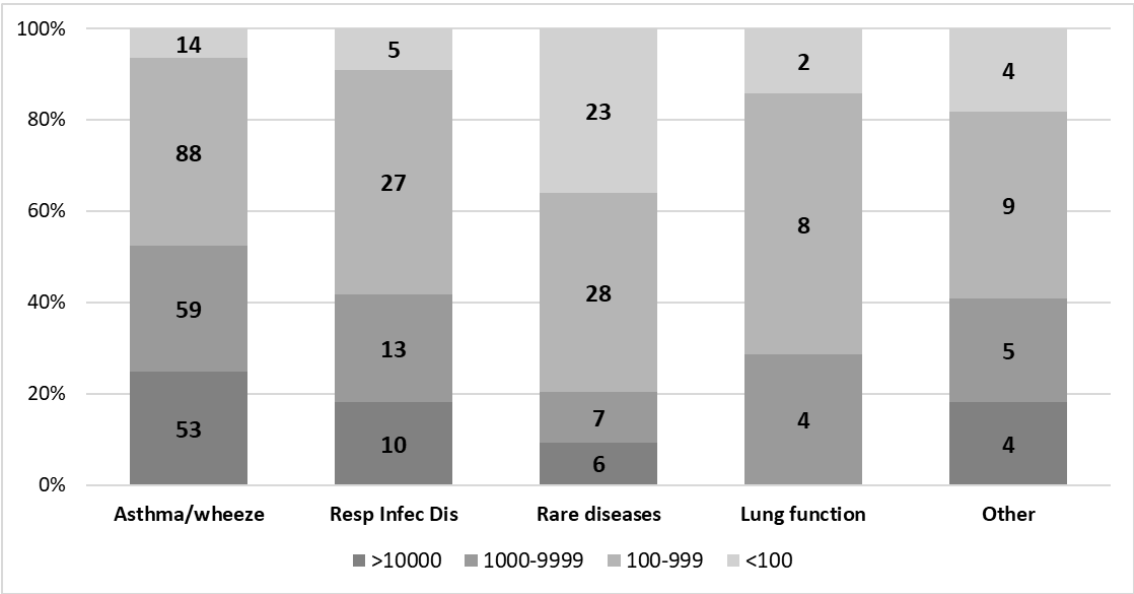


Figure 2: Type of research question (A) and sample size (B) by diagnosis of interest, of cohort studies reporting on paediatric respiratory outcomes or exposures in 2018 (N= 369).

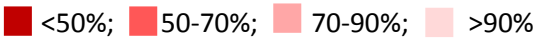
The number inside each bar is the total number of manuscripts for section.

Table 2: Number of manuscripts that accurately followed each of the STROBE checklist items for the reporting of cohort studies from a random subsample (N=100)

	Item No	Recommendation	N
Title and abstract	1	All criteria for item 1	81
		(*a*) Indicate the study's design with a commonly used term in the title or the abstract	83
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	97
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	100
Objectives	3	State specific objectives, including any prespecified hypotheses	97
Methods			
Study design	4	Present key elements of study design early in the paper	93
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	90
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	94
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	84
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	96
Bias	9	Describe any efforts to address potential sources of bias	58
Study size	10	Explain how the study size was arrived at	64
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	92
Statistical methods	12	All criteria for item 12	38
		(*a*) Describe all statistical methods, including those used to control for confounding	92
		(*b*) Describe any methods used to examine subgroups and interactions	83
		(*c*) Explain how missing data were addressed	43
		(*d*) If applicable, explain how loss to follow-up was addressed	59
		(*e*) Describe any sensitivity analyses	66
Results			
Participants	13*	All criteria for item 13 (except c)	72
		(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	78
		(b) Give reasons for non-participation at each stage	76
		(c) Consider use of a flow diagram	-
Descriptive data	14*	All criteria for item 14	56
		(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	90
		(b) Indicate number of participants with missing data for each variable of interest	59
		(c) Summarise follow-up time (eg, average and total amount)	82
Outcome data	15*	Report numbers of outcome events or summary measures over time	98
Main results	16	All criteria item 16 (except c)	82

		(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	84
		(*b*) Report category boundaries when continuous variables were categorized	98
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	85
Discussion			
Key results	18	Summarise key results with reference to study objectives	100
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	94
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	96
Generalisabil.	21	Discuss the generalisability (external validity) of the study results	51
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	84

Colour code for proportion of manuscripts that reported each item:



Items in white were not evaluated as they are not compulsory but should be only ‘considered’.

We did not evaluate item 6b as none of the studies included were matched.

Table 3: Association between studies' and journal's characteristics, and the total score on STROBE reporting recommendations for cohort studies' checklist from a multivariable Poisson regression (N=100)

	STROBE score		Poisson regression	
	Median	IQR	Crude IRR (95% CI)	Global P value[##]
Society journal: Yes	18	16-21	1.0 (0.9-1.1)	0.562
No	18	15-20		
Journal reporting recommendation				
None	17	16-18	(ref)	0.698
Follow any	19	16-21	1.1 (0.9-1.2)	
Follow STROBE	18	15-21	1.0 (0.9-1.2)	
Attach STROBE checklist	19	14-20	1.0 (0.8-1.2)	
Impact factor			1.0 (1.0-1.1)	0.387
Percentage ranking			1.0 (1.0-1.0)	0.279
Journal category[#]				
Respiratory	18	15-20	(ref)	0.762
Allergy	18	16-20	1.0 (0.9-1.2)	
Paediatrics	18	16-20	1.0 (0.9-1.2)	
General medicine	18	14-20	1.0 (0.8-1.2)	
Infectious diseases	15	15-15	0.9 (0.5-1.4)	
Pub health/epidemiology/environment	19	18-21	1.1 (0.9-1.2)	
Other	22	15-22	1.1 (0.9-1.3)	
Continent of study				
Europe	20	17-21	(ref)	0.493
North America	19	16-21	1.0 (0.9-1.1)	
South America	15	14-16	0.8 (0.6-1.1)	
Africa	16	16-18	0.9 (0.7-1.1)	
Asia	18	13-18	0.9 (0.7-1.03)	
Pacific	16	15-18	0.9 (0.8-1.1)	
Several	21	15-21	1.0 (0.8-1.3)	
Research question				
Aetiology	19	17-21	(ref)	0.078
Natural history / prognosis	18	16-20	1.0 (0.9-1.1)	
Diagnosis	14	14-14	0.7 (0.4-1.3)	
Treatment effects	16	15-17	**0.8 (0.7-0.97)**	
Main diagnosis of interest				
Asthma or wheeze	19	16-21	(ref)	0.825
Respiratory infectious diseases	18	16-18	0.9 (0.8-1.1)	
Rare diseases*	18	15-21	1.0 (0.9-1.1)	
Lung function (healthy children)	20	20-21	1.1 (0.9-1.4)	
Other**	17	16-21	1.0 (0.8-1.2)	

*Rare diseases include: bronchopulmonary dysplasia, diaphragmatic hernia, cystic fibrosis and primary ciliary dyskinesia. **Other diagnoses include: cough, respiratory distress syndrome, pneumothorax and unspecific respiratory symptoms. [#]Categories according to the InCites Journal Citation Report, if a journal appeared in 2 categories, it was classified as the first in which it appears in this order: respiratory, allergy, infectious diseases, public health/epidemiology/environment, paediatrics, general medicine and any other category. **[##]:** Estimated with the likelihood ratio test**.** IQR: inter-quartile range, RCT: randomized controlled trial.

Table 4: Association between studies' and journal's characteristics, and reporting of the 4 most poorly reported items (<60% of the manuscripts) from a multivariable logistic regression (N=100)

	Crude OR (95%CI) for reporting items			
	Item 9 (Bias)	**Item 12 (Statistics)**	**Item 14 (Descriptive)**	**Item 21 (Generalisability)**
Society journal	1.7 (0.7-3.8)	1.7 (0.7-3.9)	1.0 (0.5-2.3)	1.1 (0.5-2.4)
Journal reporting recommendation				
None	(ref)	(ref)	(ref)	(ref)
Follow any guideline	3.0 (0.9-9.5)	1.1 (0.4-3.6)	1.2 (0.4-3.8)	**3.7 (1.1-12.1)**
Follow STROBE	2.0 (0.6-6.1)	1.1 (0.3-3.4)	0.7 (0.2-2.3)	1.2 (0.4-3.8)
Attach STROBE checklist	1.4 (0.3-5.9)	0.9 (0.2-3.9)	0.7 (0.2-3.1)	1.7 (0.4-7.4)
Impact factor	1.1 (0.96-1.2)	1.1 (0.99-1.2)	1.0 (0.9-1.1)	1.1 (0.99-1.2)
Percentage ranking	1.0 (0.9-1.03)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Journal category*				
Respiratory	(ref)	(ref)	(ref)	(ref)
Allergy	2.3 (0.8-6.7)	1.6 (0.5-5.0)	1.8 (0.6-5.1)	0.6 (0.2-1.8)
Paediatrics	0.9 (0.3-3.4)	1.3 (0.3-5.1)	1.5 (0.4-5.3)	0.4 (0.1-1.6)
General medicine	0.5 (0.08-3.5)	2.6 (0.4-15.9)	1.3 (0.2-7.6)	0.3 (0.05-2.2)
Infectious diseases	-	-	-	-
Pub health/epidemiology/ environment	4.9 (0.9-27.3)	1.5 (0.3-6.6)	2.2 (0.5-9.6)	0.8 (0.2-3.3)
Other	1.3 (0.3-5.4)	4.5 (1.0-20.3)	3.4 (0.7-15.9)	1.2 (0.3-5.1)
Continent of study				
Europe	(ref)	(ref)	(ref)	(ref)
North America	0.4 (0.1-1.03)	0.5 (0.2-1.3)	0.7 (0.3-1.9)	1.4 (0.6-3.7)
South America	0.4 (0.2-6.8)	-	-	-
Africa	**0.1 (0.01-0.97)**	0.6 (0.9-4.0)	0.8 (0.1-5.7)	0.6 (0.1-4.0)
Asia	**0.2 (0.05-0.9)**	**0.1 (0.01-0.8)**	0.5 (0.1-1.8)	**0.1 (0.01-0.8)**
Pacific	1.3 (0.2-7.6)	0.5 (0.1-2.1)	**0.2 (0.02-0.9)**	3.1 (0.6-17.2)
Several	0.8 (0.06-9.5)	0.5 (0.04-5.4)	1.1(0.1-13.7)	0.5 (0.04-5.4)
Research question				
Aetiology	(ref)	(ref)	(ref)	(ref)
Natural history / prognosis	1.0 (0.4-2.4)	**0.4 (0.2-0.97)**	0.7 (0.3-1.6)	1.0 (0.4-2.4)
Diagnosis	-	-	-	-
Treatment effects	**0.2 (0.04-0.7)**	-	**0.2 (0.07-0.9)**	0.4 (0.1-1.3)
Main diagnosis of interest				
Asthma or wheeze	(ref)	(ref)	(ref)	(ref)
Respiratory infectious dis.	1.0 (0.3-3.4)	0.6 (0.2-2.0)	1.1 (0.3-3.6)	**0.2 (0.06-0.98)**
Rare diseases*	1.2 (0.4-3.7)	0.5 (0.2-1.6)	0.6 (0.2-1.7)	1.2 (0.4-3.5)
Lung function (healthy)	-	2.5 (0.2-28.7)	1.3 (0.1-15.3)	1.6 (0.1-18.9)
Other**	3.0 (0.6-15.9)	0.2 (0.2-1.3)	0.3 (0.07-1.4)	0.7 (0.2-2.7)

*Rare diseases include: bronchopulmonary dysplasia, diaphragmatic hernia, cystic fibrosis and primary ciliary dyskinesia. **Other diagnoses include: cough, respiratory distress syndrome, pneumothorax and unspecific respiratory symptoms. #Categories according to the InCites Journal Citation Report, if a journal appeared in 2 categories, it was classified as the first in which it appears in this order: respiratory, allergy, infectious diseases, public health/epidemiology/environment, paediatrics, general medicine and any other category. IQR: inter-quartile range, RCT: randomized controlled trial.

Supplementary Text

Search terms used for Medline (Ovid)

1. exp cohort studies /

2. (cohort* or prospectiv* or longitudinal* or nested or retrospectiv* or follow*).ti,ab,kw.

3. exp pediatrics/ or exp adolescent/ or exp child/ or exp infant/

4. (toddler* or infan* or child* or schoolchild* or adolescen* or teen* or pediatr* or paediatr*).ti,ab,kw

5. exp "Respiratory Tract Diseases"/ or exp "signs and symptoms, respiratory"/

6. (asthma* or wheez* or bronch* or trache* or laryng* or "vocal cord*" or "primary ciliary dyskinesia" or "cystic fibrosis" or "lung disease*" or "lung infection" or respirat* or cough* or dyspn* or pneumo* or pleura* or pulmonar* or chest or thora* or empyema or "lung abscess" or legionell* or tuberculos* or aspergill* or blastomycos* or "syncytial virus").ti,ab,kw.

7. exp Respiratory Function Tests/

8. ("Airway Resistance" or "Blood Gas Analysis" or Oximetry or Capnography or "Exercise Test*" or "Lung Compliance" or "Lung Volume" or "Lung Capacity" or Plethysmography or "Ventilation-Perfusion" or "forced expiration" or "expiratory flow" or "expiratory volume" or "Maximal Voluntary Ventilation" or "maximal expiratory" or spirometry or "Valsalva Maneuver" or "lung function" or "lung examination" or sputum or "lung biopsy" or "multiple breath washout" or "transthoracic" or "lung angiography" or "lung lavage").ti,ab,kw.

9. exp respiration/

10. (breathing or "breath holding" or exhalation or inhalation or "mucociliary clearance" or "lung clearance" or "lung diffusion" or "lung gas exchange" or "lung mechanics" or "lung ventilation").ti,ab,kw.

11. 1 or 2

12. 3 or 4

13. 5 or 6 or 7 or 8 or 9 or 10

14. 11 and 12 and 13

15. limit 14 to english language

16. limit 15 to year=’2018’

TOTAL: 7610 references

Supplementary Table 1: Classification of journals according to the categories used by the In Cites Journal Citation Report.

Respiratory	- American Journal of Respiratory & Critical Care Medicine - Annals of the American Thoracic Society - BMC Pulmonary Medicine - ERJ Open Research - European Respiratory Journal - International Journal of Tuberculosis & Lung Disease - Journal of Asthma - Journal of asthma and allergy - Journal of Cystic Fibrosis - Journal of Thoracic Disease - NPJ Primary Care Respiratory Medicine - Pediatric Pulmonology - Respiratory Care - Respiratory Medicine - Respiratory Physiology & Neurobiology - Respiratory Research - The Lancet Respiratory Medicine - Thorax
Allergy/immunology	- Allergologia et Immunopathologia - Allergology International - Allergy - Allergy & Asthma Proceedings - Allergy: European Journal of Allergy and Clinical Immunology - Annals of Allergy, Asthma, & Immunology - Asian Pacific Journal of Allergy & Immunology - Asim, Allerji, Immunoloji - Clinical & Experimental Allergy - Journal of Allergy & Clinical Immunology - Journal of Allergy & Clinical Immunology: In practice - Journal of Immunology - Journal of Investigational Allergology & Clinical Immunology - Pediatric Allergy & Immunology - World Allergy Organization Journal
Epidemiology, public health and environmental	- American Journal of Epidemiology - BMC Public Health - Clinical Epidemiology - Epidemiology - Epidemiology & Infection - European Journal of Epidemiology - International Journal of Epidemiology - Iranian Journal of Allergy Asthma & Immunology - Journal of Epidemiology & Community Health - Public Health - Archives of Environmental & Occupational Health - Atmospheric Environment - Environment International - Environmental Epidemiology - Environmental Health Perspectives - Environmental Health: A Global Access Science Source - Environmental Research - Environmental Science & Pollution Research - International Journal of Environmental Research & Public Health

	- Science of the Total Environment
Paediatrics	- Acta Paediatrica - American Journal of Perinatology - Archives of Disease in Childhood - BMC Pediatrics - BMJ Paediatrics Open - Clinical Pediatrics - Early Human Development - Egyptian Pediatric Association Gazette - European Journal of Pediatrics - International Journal of Pediatrics - Jornal de Pediatria - Journal of Adolescent Health - Journal of Pediatrics - Journal of Perinatology - Maternal & Child Health Journal - Minerva Pediatrica - Neonatology - Paediatrics & Child Health - Pediatric Research - Pediatrics - Pediatrics & Neonatology - Prenatal Diagnosis - Revista Paulista de Pediatria - The Lancet Child & Adolescent Health
Infectious diseases	- AIDS Research & Human Retroviruses - Antibiotics - Clinical Infectious Diseases - Emerging Infectious Diseases - European Journal of Clinical Microbiology & Infectious Diseases - Journal of Infectious Diseases - Journal of Medical Virology - Journal of Microbiology, Immunology & Infection - Open Forum Infectious Diseases - Pediatric Infectious Disease Journal - Vaccine
General Medicine	- African Health Sciences - BioMed Research International - Bjgp Open - BMJ Open - Bosnian Journal of Basic Medical Sciences - Colombia Medica - Cureus - Eastern Mediterranean Health Journal - eLife - Eurosurveillance - International journal of general medicine - JAMA Pediatrics - Jci Insight - Nature Communications - PeerJ - PLoS ONE - Revista Da Associacao Medica Brasileira - Sao Paulo Medical Journal = Revista Paulista de Medicina - Saudi Medical Journal - Scientific Reports - Southern Medical Journal

Other	- Acta Obstetricia et Gynecologica Scandinavica - American Journal of Clinical Nutrition - American Journal of Managed Care - American Journal of Obstetrics & Gynecology - American Journal of Respiratory Cell & Molecular Biology - American Journal of Tropical Medicine & Hygiene - Annals of Behavioral Medicine - Annals of Surgery - Arthritis care & research - British Journal of Dermatology - British Journal of Nutrition - CJEM Canadian Journal of Emergency Medical Care - Clinical Nutrition - Clinical Otolaryngology - ClinicoEconomics and Outcomes Research - CMAJ - European Journal of Clinical Nutrition - European Journal of Obstetrics, Gynecology, & Reproductive Biology - European Journal of Psychotraumatology - European Radiology - Frontiers in Pharmacology - Frontiers in Physiology - Health Promotion Practice - Health Services Insights - Hypertension - International Journal of Eating Disorders - Journal of Laparoendoscopic & Advanced Surgical Techniques. - Journal of Pediatric Gastroenterology & Nutrition - Journal of Pediatric Nursing - Journal of Pediatric Surgery - Journal of Racial & Ethnic Health Disparities - Journal of Voice - Maternal & Child Nutrition - Metabolomics - Nature Plants - Nutrients - Oncotarget - Orphanet Journal Of Rare Diseases - Pediatric Critical Care Medicine - Pharmacoepidemiology & Drug Safety - Postepy Dermatologii I Alergologii - Psychology & Health - Ultrasound in obstetrics & gynecology

Supplementary Table 2: Characteristics of cohort studies reporting on paediatric respiratory outcomes or exposures in 2018, by journal categories (N=369)

	Respira-tory (N=103)	Allergy/ Immun (N=88)	Resp. infect dis. (N=14)	PH /epi /envir. (N=37)	Paedia-trics (N=57)	General med. (N=23)	Other (N= 47)
Location							
Europe	45 (44)	40 (45)	3 (21)	17 (46)	23 (40)	6 (26)	27 (57)
North America	31 (30)	21 (24)	6 (43)	9 (24)	23 (40)	6 (26)	12 (26)
South America	2 (2)	3 (3)	0	0	3 (5)	4 (17)	0
Africa	4 (4)	5 (6)	0	3 (8)	1 (2)	3 (13)	1 (2)
Asia	6 (6)	14 (16)	2 (14)	4 (11)	3 (5)	4 (17)	4 (9)
Pacific	10 (10)	4 (5)	3 (21)	3 (8)	4 (7)	0	3 (6)
Several continents	5 (5)	1 (1)	0	1 (3)	0	0	0
Sample size (median, IQR) (N= 367)	564 (144-3277)	769 (250-2892)	1403 (158-15504)	3537 (641-23100)	701 (145-4475)	432 (77-10476)	664 (161-9038)
Sample size category (N= 367)							
<100	20 (19)	5(6)	1 (7)	1 (3)	8 (14)	6 (26)	7(15)
100 - 999	42 (41)	46 (52)	5 (36)	11 (30)	26 (46)	8 (35)	22(47)
1 000 – 9 999	28 (27)	25 (28)	4 (29)	11 (30)	10 (18)	3 (13)	7(15)
≥ 10 000	13 (13)	12 (14)	4 (29)	14 (38)	13 (23)	6 (26)	11(23)
Study design							
Birth/pregnancy cohort	44 (43)	42 (48)	2 (14)	20 (54)	22 (39)	5 (22)	17(36)
Population-based (after birth)	12 (12)	10 (11)	2 (14)	10 (27)	8 (14)	6 (26)	8(17)
Clinical cohort (prospective)	31 (30)	28 (32)	9 (64)	6 (16)	14 (25)	7 (30)	14(30)
Retrospective chart review	13 (13)	0	0	0	12 (21)	4 (17)	6(13)
Nested case-control	1 (1)	3(3)	1(7)	0	0	1 (4)	1(2)
RCT with continued follow-up	2 (2)	5 (6)	0	1(3)	1 (2)	0	1(2)
Linkage with routine data(N= 367)	18(18)	19 (22)	5 (36)	10 (27)	13 (23)	5 (22)	15(32)
Research question							
Aetiology	42(41)	50 (57)	4 (29)	27 (73)	27 (47)	15 (65)	29(62)
Natural history / prognosis	40(39)	28 (32)	7 (50)	4 (11)	20 (35)	4 (17)	13(28)
Diagnosis	4 (4)	0	0	0	0	0	0
Treatment effects	17(17)	8 (9)	3 (21)	5 (14)	10 (18)	4 (17)	5 (11)
Aetiology	0	2 (2)	0	1 (3)	0	0	0
Main diagnosis of interest							
Asthma or wheeze	56 (54)	72 (82)	1(7)	25 (68)	22 (39)	13 (57)	25(53)
Respiratory infectious dis.	7 (7)	11 (13)	9 (64)	5 (14)	14 (25)	4 (17)	5 (11)
Rare diseases*	27(26)	0	4 (29)	0	16 (28)	4 (17)	13(28)
Lung function (healthy)	7 (7)	1 (1)	0	4 (11)	0	0	2 (4)
Other**	6 (6)	4 (5)	0	3 (8)	5 (9)	2 (9)	2 (4)

IQR: inter-quartile range, RCT: randomized controlled trial, CF: cystic fibrosis, PCD: Primary ciliary dyskinesia.

11 Other activities

11.1 Pafu Changa

Diana Mwendwa Marangu visited the Institute of Social and Preventive Medicine for a research stay with funding from a European Respiratory Society scholarship in October-December 2019. The aim for her research stay was to plan a cohort study for investigating sickle cell lung disease in children in Kenya, the Pafu Changa. The study will be a prospective longitudinal cohort study including children and adolescents aged <18 years with sickle cell lung disease on follow up at the Kenyatta National Hospital. The study design share similarities with the SPAC study, and I therefore gave inputs for the ethics application, the design of study documents, and on pitfalls that we encountered while setting up the SPAC study. Diana Mwendwa Marangu is currently writing a draft of a study protocol of which I am a planned co-author.

11.2 European study on physical activity and asthma development in childhood

The European study on physical activity and asthma development in childhood is a collaborative study between 25 European cohort studies, and the project is led by Marianne Eijkemans from the Maastricht University. The study aims to examine the association between physical activity and the development of asthma in childhood. The study uses data on physical activity from questionnaires, diaries, and accelerometers, and data on wheeze and asthma from patient questionnaires and hospital records if available. I was responsible for preparing and sending data from the LRC study to Marianne Eijkemans, who analysed and interpreted the data from all the cohorts. I sent the final dataset in October 2018, and the manuscript is currently being drafted.

12 Acknowledgements

Thanks to my supervisor, Claudia Kuehni, for the opportunity to do this PhD and for teaching me good research practice and critical thinking.

Thanks to my co-referee, Alexander Moeller, for giving good clinical inputs.

Thanks to my mother and the rest of my family for always being at the other end of the phone, for sending packages from Denmark and for being loving and always supportive.

Thanks to Lisa Lorentzen back home in Copenhagen for being my steady support-rock over the last four years.

Thanks to my special partner in crime, Carmen de Jong. Thanks to the two postdocs Myrona and Cristina for all their help. Thanks to the past and present wonderful respi-group members: Maja, Jingying, Florian, Myrona, Rebeca, Agatha, Christina, Eugenie, Diana. And thanks to our good friends in the cancer, spatial epi, and cardiometabolic health groups: Annette, Rahel, Fabienne, Nic, Maria, Carole, Sven, Akis, Antonella, Christoph, Astrid, and Sanne. Thanks to our parallel PhD friends from Insel, among others Andras, Johanna, and Corin. And thanks to Käthi for always being ready to help.

Thanks to all the people at the clinics who helped make the SPAC study possible.

Thanks to Chris Ritter for being a great language inspiration

And thanks to Corsin for taking my mind of the PhD every weekend with plenty of spaghetti, adventures in the mountains, and lots of big fish. FYI: Fishes are not pets!

13 Curriculum Vitae / Publication list

Eva Pedersen **CURRICULUM VITAE** **January 2020**

Personal information

Name	**Eva Sophie Lunde Pedersen**
Address	Forstweg 56, 3012 Bern
Date and place of birth	11th February 1986, Viborg (Denmark)
Nationality	Danish
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E-Mail	Eva.pedersen@ispm.unibe.ch
ORCID ID	https://orcid.org/0000-0003-0293-9954

Present Appointment

Since 04.2016	**PhD Candidate in paediatric asthma epidemiology** University of Bern - Institute for Social and Preventive Medicine. Switzerland

Previous appointments

May 2015-March 2016	**Research assistant in exercise epidemiology** National Institute of Public Health, Copenhagen. Denmark
Sep 2014-April 2015	**Master student: Validation of physical activity questionnaire** Centre for Prevention and Health, Glostrup. Denmark.
Sep 2013-April 2015	**Student assistant: National study of dietary habits and physical activity** Technical University of Denmark, Copenhagen. Denmark
Jan 2013-Jun 2013	**Internship: Drugs and chronic infectious diseases in Germany** Robert Koch Institute, Berlin. Germany
Sep 2010-Jan2011	**Student assistant: Risk of inflammatory bowel disease and childhood vaccinations** Bispebjerg hospital, Copenhagen. Denmark

Academic and professional qualifications

Apr 2016-Mar 2020	PhD students, University of Bern
Sep 2012-May 2015	Master in Public Health, University of Copenhagen
Sep 2009-Jun 2012	Bachelor in Public Health, University of Copenhagen
Sep 2007-Nov 2008	Bachelor in Sports Science, University of Southern Denmark (first year)

Languages and computer skills

Language	Danish: Mother tongue
	English: For professional use
	German: For professional use
	Swiss German: For professional use
Computer skills	SPSS, sas, STATA, R
	Microsoft word, excel, outlook
	Endnote

Other appointments

2010-2014	Waitressing and bartending, Copenhagen
2011 – 2012	Volunteering at Café Retro, a non-profit organisation to raise money for projects in Sierra Leone,
2008 - 2014	Hay making assistant, farm, Swiss alps
2004-2006	Gymnastics instructor, children and elderly

Research activity/publication list

Original articles (Peer-reviewed journals)

First-author

Pedersen ESL, Spycher BD, de Jong CCM, Halbeisen F, Ramette A, Gaillard EA, Granell R, Henderson AJ, Kuehni CE. *The Simple 10-Item Predicting Asthma Risk in Children Tool to Predict Childhood Asthma-An External Validation.* J Allergy Clin Immunol Pract. 2019 Mar;7(3):943-953.e4. doi: 10.1016/j.jaip.2018.09.032.

Pedersen ESL, de Jong CCM, Ardura-Garcia C, Barben J, Casaulta C, Frey U, Jochmann A, Latzin P, Moeller A, Regamey N, Singer F, Spycher B, Sutter O, Goutaki M, Kuehni CE. *The Swiss Paediatric Airway Cohort (SPAC).* ERJ Open Res. 2018 Nov 20;4(4). pii: 00050-2018. doi: 10.1183/23120541.00050-2018. eCollection 2018 Oct.

Pedersen ESL, Mortensen LH, Brage S, Bjerregaard AL, Aadahl M. *Criterion validity of the Physical Activity Scale (PAS2) in Danish adults*. Scandinavian journal of public health. 2017:1403494817738470

Pedersen ES, Danquah IH, Petersen CB, Tolstrup JS. *Intra-individual variability in day-to-day and month-to-month measurements of physical activity and sedentary behaviour at work and in leisure-time among Danish adults*. BMC public health. 2016;16(1):1222

Co-author

de Jong CCM, **Pedersen ESL**, Goutaki M, Trachsel D, Barben J, Kuehni CE. Diagnosis of asthma in children: the contribution of a detailed history and test results.The European respiratory journal. 2019; DOI: 10.1183/13993003.01326-2019

de Jong CCM, **Pedersen ES**, Goutaki M, Trachsel D, Barben J, Kuehni CE. *Do clinical investigations predict long-term wheeze? A follow-up of pediatric respiratory outpatients*. Pediatr Pulmonol. 2019 Apr 26. doi: 10.1002/ppul.24347

Danquah IH, **Pedersen ESL**, Petersen CB, Aadahl M, Holtermann A, Tolstrup JS. *Estimated impact of replacing sitting with standing at work on indicators of body composition: Cross-sectional and longitudinal findings using isotemporal substitution analysis on data from the Take a Stand! study*. PloS one. 2018;13(6):e0198000.

Spycher BD, Cochrane C, Granell R, Sterne JAC, Silverman M, **Pedersen E,** et al. *Temporal stability of multitrigger and episodic viral wheeze in early childhood*. The European respiratory journal. 2017;50(5)

Research letters

Pedersen ESL, de Jong CC. Addressing selection bias in diagnostic accuracy studies. Pediatr Int. 2019 Aug;61(8):840. Doi: 10.111/ped.13860.

Mozun R**, Pedersen ESL**, Ardura-Garcia C. Does high-flow oxygen reduce escalation of care in infants with hypoxaemic bronchiolitis?. Breathe (Sheff). 2019 Sep; 15(3):247-249. Doi: 10.1183/20734735.0192-2019

Ardura-Garcia C, **Pedersen ESL,** Goutaki M. *The limitations of cross-sectional data: perinatal risk factors for asthma*. Eur Respir J. 2018 Sep 6;52(3). pii: 1801197. doi: 10.1183/13993003.01197-2018. Print 2018 Sep

Congress Participation

European Respiratory Society annual congress	2016 London 2017 Milano 2018 Paris 2019 Madrid
Swiss Society of Paediatrics annual congress	2017 St. Gallen 2018 Lausanne
Swiss Public Health conference	2018 Neuchatel 2019 Winterthur

Awards

2018	Prize for best presentation on the SwissPedNet Translational and clinical research session, Lausanne, May 24th 2018
2017	Young researchers' SwissPedNet travel award: Visit to Asthma and Allergy Research Group in Munich, Germany, from March 26-29, 2017.

Teaching activity

Co-supervision of master thesis of medical students	Anja Lehmann (main supervisor: Claudia Kuehni). Title of master thesis: Prevalence of asthma and asthma related symptoms Lara Quinten (main supervisor: Claudia Kuehni). Title of master thesis: Physical activity in children
Problem based learning (PBL) tutor for medical students	Spring 2019: Embryology, epidemiology Fall 2019: Biomedical statistics
Tutor for medical students	Fachpraktikum: Critical appraisal 2018: Led by Sven Trelle 2019: Led by Cristina Ardura and Myrofora Goutaki
Tutor for master in public health (MPH) students	Spring 2017. Course: Introduction to Epidemiology and Study Designs, led by Marcel Zwahlen and Claudia Kuehni

Development of multiple choice exam questions for medical students	Topics: epidemiology and statistics

Review activities for journals

11 reviews	European Respiratory Journal
1 review	European Journal of Pediatrics
1 review	Plos One
1 review	Electronic Journal of General Medicine
1 review	European Journal of Epidemiology

Course list

June 20th 2017	Project Management – completing your research project professionally and timely
Sep 6th – 8th 2017	Writing a Journal Article… and Getting it Published
April 26th – 28th 2017	Understanding Health Inequalities in Modern Societies: From Contemplation to Implementation, Spring school of public health
June 6th 2017	Classical paper journal club - ISPM
May 18th – 22nd 2017	Introduction to Epidemiology and study designs, University of Bern
Jan 16th – 18th 2017	Statistical Analysis with missing data using multiple and inverse probability weighting. Swiss epidemiology winter school.
Jan 19th – 21st 2017	Assessing Bias in randomized and non-randomized studies: new approaches, new tools. Swiss epidemiology winter school.
May 8th 2017	Essential Medical Statistics, ISPM
May 10th – 12th 2017	Systematic reviews and meta-analysis, a practical approach, ISPM
Oct 9th – 11th 2017	Multilevel Modelling: Analysis of Clustered Data
May 2017 – Jan 2018	Book Club/Seminar: Epidemiology
Oct 17th 2018	Clinical Investigators 1: basic GCP and clinical research training
Jan 18th – 20th 2018	Prognostic Research: From Basics to Modelling
September 27th – 28th 2018	Using DAGs for Causal Inference
November 27th – 30th 2018	Fundamental Concepts in Epidemiology
January 21st – 23rd 2019	Causal Inference in Observational Epidemiology
January 24th – 26th 2019	Digital Epidemiology and Participatory surveillance

14 Declaration of originality

Declaration of Originality

Last name, first name: Pedersen, Eva Sophie Lunde

Matriculation number: 15-135-056

I hereby declare that this thesis represents my original work and that I have used no other sources except as noted by citations.

All data, tables, figures and text citations which have been reproduced from any other source, including the internet, have been explicitly acknowledged as such.

I am aware that in case of non-compliance, the Senate is entitled to withdraw the doctorate degree awarded to me on the basis of the present thesis, in accordance with the "Statut der Universität Bern (Universitätsstatut; UniSt)", Art. 69, of 7 June 2011.

Place, date

Bern, 16.01.2020

Signature