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

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Running title

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Abstract (250/250 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 primary care physician with the final diagnosis from the outpatient clinic and described diagnostic tests and treatments.

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

Patients: We included children with EIS as main reason for referral. Information about diagnostic investigations, final diagnosis, and treatment prescribed came from outpatient records. We included 214 children (mean age 12 years, range 2-17, 54% males) referred for EIS.

Results: 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%, 95%-CI 46-60%). Spirometry, body plethysmography, and exhaled nitric oxide were performed in almost all, exercise-challenge tests in a third, and laryngoscopy in none. 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 proposed by the referring physician. Diagnostic evaluations, management,

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and follow-up differed between clinics and diagnostic groups highlighting the need for evidence-based diagnostic guidelines and harmonised procedures for children seen for EIS.

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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 can be indicative of ILO.[13-15] Cardiopulmonary exercise testing monitors gas exchange during exercise and is typically used for proving hyperventilation or an insufficient fitness level. Flexible laryngoscopy allows

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to directly visualise laryngeal function during exercise.[1] There are however no comprehensive international guidelines that recommend which tests should be used and in which order. Published recommendations focus on a single aetiology, such as exercise-induced bronchoconstriction.[16] Most clinics use only a selection of diagnostic tests based on availability and personal interest of the physicians. This leads to variability in diagnostic practices among clinics.

Delayed or faulty diagnosis can lead to physical activity avoidance,[17,18] reduced quality of life,[19] and overtreatment with inhaled corticosteroids if mistakenly diagnosed as asthma.[6,20] Only few studies have investigated diagnostic practices, diagnoses given, and treatment prescribed to children seen for EIS[7,20-24], and all have focused on selected groups of patients usually after excluding those with asthma. No studies have compared referring diagnosis with diagnosis given at specialised respiratory clinics. This study aimed to describe the current situation of diagnostic evaluation and management of EIS in children in the German speaking part of Switzerland by describing the handling of this problem in respiratory outpatient clinics of paediatric teaching hospitals. We wanted to describe how often the investigations performed in the specialized setting changed the referring primary care physician's diagnosis, but also to investigate the types and consistency of tests used at the five pulmonary clinics to arrive at differential diagnosis and to review treatment prescribed before the respiratory outpatient clinic visit. This knowledge is important to understand the relevance of specific investigations, but also to understand shortcomings of current practice and the need for possible harmonization and improvement.

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Methods

Study design

We used data from the Swiss Paediatric Airway Cohort (SPAC), an observational national multi-centre clinical cohort from Switzerland (www.spac-study.ch).[25] The SPAC study describes the clinical picture of outpatients but also diagnostic evaluations, prescribed treatments, and long term outcomes of all children (aged 0-16 years) who are referred to the paediatric respiratory outpatient clinic of participating hospitals for respiratory problems such as wheeze, cough, dyspnoea, sleep- or exercise-related symptoms. This analysis focused on a sub-cohort, namely all those referred specifically for evaluation of exercise-induced symptoms. The SPAC study is observational; no diagnostic evaluations are done specifically for the study. Management is done as clinically indicated at each clinic, and diagnostic tests are documented in the database. Recruitment for SPAC started on 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.[26]

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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.[27]

Inclusion criteria

We included children who were referred to the paediatric outpatient clinics with EIS as main referral reason. EIS was defined as the main reason for referral if the letter sent by the referring physician described EIS as the only or main reason for referral (**E-table 1**). We excluded children with a missing referral letter or missing letter from the outpatient clinic with information on final diagnosis.

Referral diagnosis

Referral diagnosis was the diagnosis described as cause of EIS in the referral letter from the referring physician. Reasons for referral differed between primary care physicians. For example, some referred children when they first presented with exercise-induced symptoms and did not make a presumptive diagnosis while others referred children who did not respond well to asthma treatment. Suspected referral

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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). The diagnosis was based on medical history, clinical examination, and all test results from objective tests performed at the clinic. 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 (**E-table 1**). Even in children who had received a set of diagnostic tests, the final diagnosis in the clinic was often described as "suspected". For the analysis, we categorised the diagnosis as suspected if the word "suspected" was included in the diagnosis given in the outpatient clinic.

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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 [16,28,29]. 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 [30], defining overweight as BMI z-score > 1

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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 described demographics, referral diagnosis, final diagnosis, diagnostic tests, and treatment prescribed using proportion and percentages for categorical variables and means and standard deviations (SD) for continuous variables. 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 (**E-figure 1**). 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, age range 2-17 years) and 115 (54%) were male (**table 2**). The most common referral diagnosis was asthma in 126 (59%); 12 (6%) were suspected to have DB, and 74 (35%) were referred with EIS of unknown aetiology. Eighty-nine (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).

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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**). The final diagnosis was described as suspected most often for children diagnosed with asthma plus DB (n=16, 70%) and least often for children diagnosed with thoracic DB (n=7, 32%) (**table 2**). 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**). 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 unknown diagnosis at referral, 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**). A methacholine challenge test was performed in 50 (23%) and an exercise challenge in 80 (37%). Cardiopulmonary exercise tests or flexible laryngoscopy were

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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%). Fourty-two 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 most common final diagnoses apart from asthma were extrathoracic and thoracic DB, but often the final diagnosis was described as suspected, indicating remaining uncertainty of specialists. Relative frequency of final diagnoses and the set of diagnostic tests performed differed between clinics reflecting the lack of guidelines.

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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 weakness resulting from the observational real-life study design is that diagnostic evaluations and description of final diagnosis were not standardised between clinics. The final diagnosis reported in the outpatient clinic letter was described as suspected in 97 (45%) children, indicating remaining uncertainty in the final diagnosis even after the specialist consultation. In these children, the final diagnosis may change in the future based on response to treatments or further tests. The limited use of cardiopulmonary exercise testing and lack of specific invasive tests to diagnose extrathoracic DB such as flexible laryngoscopy adds to the uncertainty of diagnosis. These diagnoses were made by ruling out asthma rather than performing a specific conclusive test. The final diagnosis was made by the responsible physician based on all available test results. The selection of diagnostic tests also reflects personal preferences which vary between physicians. This might explain the variability in frequency of diagnosis between clinics.

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

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unlikely to be caused by asthma **(E-table 2)**.[7,20-22,24,31] 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.[7,22] In our study, none were diagnosed with normal physiological response to exercise, but ten children were diagnosed with insufficient fitness level. Compared to these two previous studies which did exercise-challenge tests in all children, only around half of the children in our population had an exercise-challenge test performed. This difference might partly explain why more children in previous studies were diagnosed with normal physiological response to exercise than in our study. 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

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asthma were done in a minority of children. Exercise challenge testing, recommended to reproduce symptoms in patients with EIS,[4,16,32] 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.[12,33-35] Therefore the prevalence of extrathoracic and thoracic DB might be under- or overestimated in our study. The same applies to insufficient fitness level. The tests are time consuming and costly and are thus not done on a regular basis in general respiratory outpatient clinics outside of a funded study. 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. The difference in diagnostic procedures between clinics may also partly explain the difference in the distribution of final diagnoses given at the clinics. In clinic 4, more children were diagnosed with asthma + DB (27%) compared to most other clinics in which around 10% were diagnosed with asthma + DB. All this indicate the need for more standardised approaches and recommendations for the evaluation of exercise-induced symptoms. A validated evidence-based diagnostic algorithm based on standardised prospective studies would be useful.

Prescribed treatments were less consistent between clinics and with final diagnosis than we would have expected. We would have expected that 100% of the children diagnosed with asthma would have been prescribed some sort of bronchodilator, at

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least for exercise, but in our study, it was only in 93%. In contrast also 20% of patients diagnosed with extrathoracic DB alone were prescribed SABA. This was unexpected but could indicate diagnostic uncertainty. For DB, physiotherapy or speech therapy are recommended treatments.[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 paediatric pulmonologist considered the disease as mild and selected a wait-and-see policy after careful instructions about the benign aetiology of the symptoms. This could also be due to the lack of therapists specialised on this topic in some regions. We compared treatment prescribed before and after the outpatient clinic visit and found that of the 35 children finally diagnosed with extrathoracic DB, 10 (29%) had received SABA + ICS before. We do not have information on how long these children had taken SABA + ICS before the outpatient clinic visit and therefore cannot ascertain if these children received unnecessary treatment or only a short trial treatment to assess response. However, it emphasizes the importance of referring children with EIS for further evaluation. In children finally diagnosed with thoracic DB, only 1 child had received ICS prior to the outpatient clinic visit. 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. This was also unexpected and might again reflect a lack of experience in handling these cases.

In summary, we found that final diagnosis given at the outpatient clinic differed in half of the children from the suspected referral diagnosis highlighting the importance of specialist evaluations. Extrathoracic and thoracic DB were common diagnoses in

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children with EIS but had rarely been suspected by the referring physician and were also not well followed up. Increased awareness both among primary care physicians and among respiratory specialists of how common DB are in children with EIS might lead to faster referral to specialised clinics and better treatment. Diagnostic evaluation, management and follow-up were inconsistent between clinics and diagnostic groups which highlights the need for evidence-based data, diagnostic guidelines, and harmonised procedures for children seen for exercise-induced symptoms.

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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

Dr. Singer reports personal fees from Novartis, personal fees from Vertex, outside the submitted work. All other 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

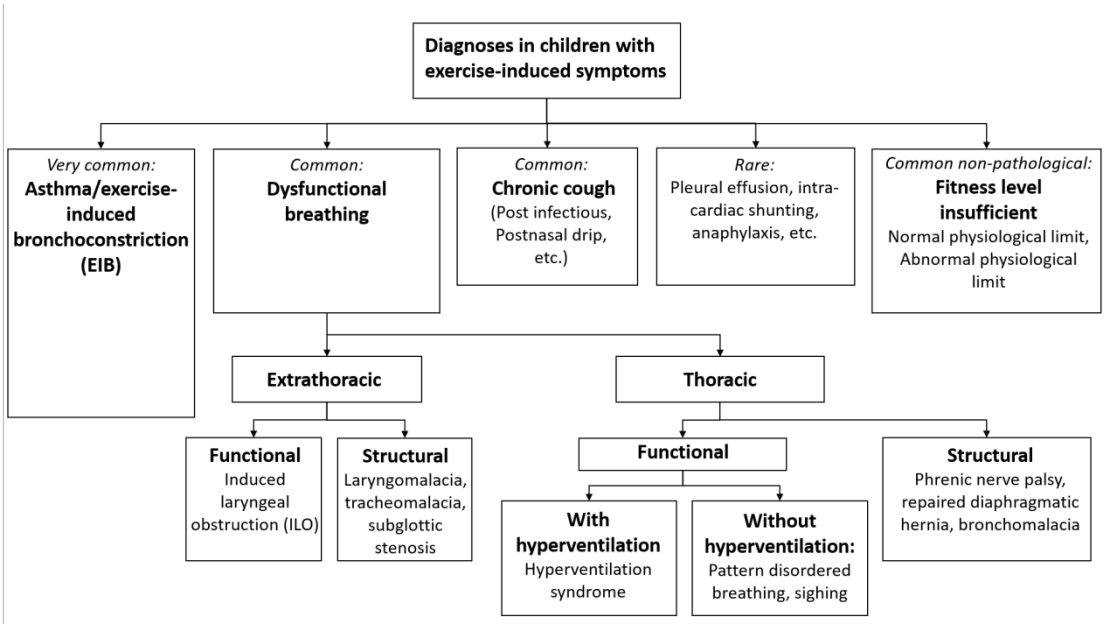

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Figure 2: Distribution of suspected referral diagnosis (suspected asthma, suspected dysfunctional breathing (DB), unknown aetiology) and final diagnosis (asthma, dysfunctional breathing (DB), asthma + DB, other) with proportions (white, grey, black) indicating relationship between suspected referral diagnosis and final diagnosis.

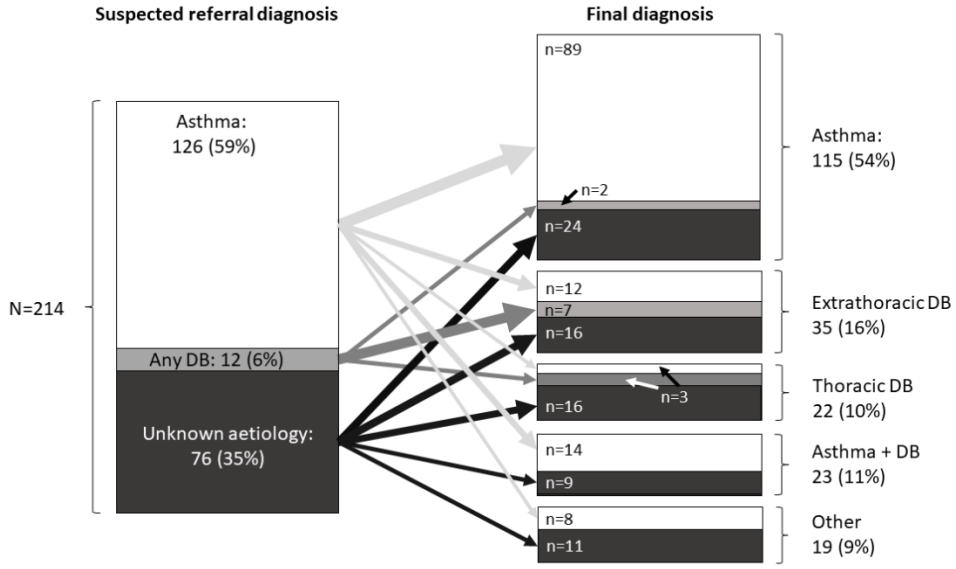

Table 1: Suspected referral diagnosis, final diagnosis, and diagnostic tests described in outpatient clinic letter, in total and by centre (N=214)

	Total	Clinic1	Clinic2	Clinic3	Clinic4	Clinic5
	N=214	N=71	N=56	N=33	N=26	N=28
Referral diagnosis (n=214)						
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
Unknown aetiology	76 (35)	26 (37)	14 (25)	15 (45)	6 (23)	15 (54)
Final diagnosis from clinic (n=214)						
Asthma	115 (54)	37 (52)	33 (59)	12 (36)	16 (62)	17 (61)

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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)
Other[a]	19 (9)	9 (13)	4 (7)	2 (6)	1 (4)	3 (11)
Final diagnosis described as suspected in clinical letter (n=214)	97 (45)	35 (49)	21 (37)	12 (38)	8 (31)	21 (75)
Diagnostic tests done at 1st visit (n=214)						
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=208)	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 (n=214)						
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)

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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]Insufficient fitness level, Chronic cough, EIS of unclear aetiology, Pleural effusion

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 (male)	115 (54)	71 (62)	12 (34)	10 (45)	7 (30)	15 (79)	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
Mother tertiary education[b] (n=198)	59 (30)	34 (32)	8 (24)	9 (45)	4 (19)	4 (22)	0.301
Father tertiary education[b] (n=197)	80 (41)	48 (45)	12 (36)	5 (28)	9 (43)	6 (33)	0.856
Referral reason							
Asthma/EIB	126 (59)	89 (77)	12 (34)	3 (14)	14 (61)	8 (42)	c
Dysfunctional breathing	12 (6)	2 (2)	7 (20)	3 (14)	0	0	
Unknown aetiology	76 (35)	24 (21)	16 (46)	16 (73)	9 (39)	11 (58)	

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Final diagnosis described as suspected in clinical letter	97 (45)	41 (36)	22 (63)	7 (32)	16 (70)	11 (58)	0.002
Diagnostic tests done at 1st visit[d]							
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
Asthma treatment prior to first visit[e]							c
No prior 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)	

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ICS only	4 (2)	2 (2)	0	1 (5)	0	1 (5)	
SABA + ICS+/-LABA	70 (33)	48 (42)	10 (29)	0	8 (35)	4 (21)	
Treatment prescribed at clinic							
No inhaled treatment prescribed	73 (34)	8 (7)	28 (80)	20 (91)	4 (17)	13 (68)	<0.001
SABA only	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[f]	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 nitric 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]Degree from university of applied sciences or university [c]too many degrees of freedom and too few observation in single cells to calculate p-value [d]Information extracted from first and second outpatient clinic letter [e]Information extracted from referral letters and first outpatient clinic letter [f]Cardiology, endocrinology, allergology, other

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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)
Other	
Insufficient fitness level	
Insufficient fitness level	10 (5)
Chronic cough	
Chronic cough unknown aetiology	4 (2)
Post-infectious chronic cough	2 (1)
Other diagnoses	
Bilateral pleural effusion	1 (0)
Unknown aetiology	2 (1)

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