Digital Comprehensive Summaries of Uppsala Dissertations
from the Faculty of Medicine 2205

Airway responses to exercise in adolescents

Epidemiology, inflammation markers and pulmonary function testing

KARIN ERSSON

ACTA UNIVERSITATIS
UPSALIENSIS
2025

ISSN 1651-6206
ISBN 978-91-513-2644-3
urn:nbn:se:uu:diva-568684

UPPSALA
UNIVERSITET

Dissertation presented at Uppsala University to be publicly examined in H:som Holmdahl, Uppsala University Hospital/Akademiska sjukhuset, Entrance 100, Uppsala, Friday, 5 December 2025 at 09:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in English. Faculty examiner: Professor Hege Clemm (Norwegian School of Sport Sciences).

Abstract

Ersson, K. 2025. Airway responses to exercise in adolescents. Epidemiology, inflammation markers and pulmonary function testing. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 2205. 75 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-2644-3.

Background: Airway disorders related to exercise are common in adolescents but remain underrecognized. This thesis investigates the prevalence, course, and characteristics of exercise-induced bronchoconstriction (EIB) and exercise-induced laryngeal obstruction (EILO) in adolescent athletes as well as postexercise airway responses in athlete and nonathlete adolescents focusing on aspects of airway physiology and inflammation.

Aim: The aim was to improve understanding of exercise-related airway responses in adolescents using epidemiological, clinical, and biomarker approaches. Objectives included assessing the prevalence and course of EIB and EILO in athletes, examining links between symptoms, fractional exhaled nitric oxide (FeNO), and postexercise airway responses in athletes and nonathletes, and exploring associations between systemic inflammation proteins, lung function, and airway responses in nonathletes.

Methods: Two adolescent groups were studied: athletes from a national sports high school (N=98) and nonathletes from the general population (N=143). All completed questionnaires, exercise challenge tests, FeNO measurement, and lung function assessment by spirometry and oscillometry; nonathletes also underwent plasma proteomic analysis. Studies I–II examined EIB and EILO prevalence and progression in athletes; Study III explored links between symptoms, FeNO, and postexercise airway responses in both groups; Study IV investigated associations between inflammatory proteins, lung function, and airway responses in nonathletes.

Results: Estimated EIB prevalence among athletes was 23% (95% confidence interval (CI) 14.5–33.8) and EILO 8% (95% CI 2.5–18.5). Self-reported exercise-induced dyspnea poorly predicted either condition. Both EIB and EILO were dynamic over two years. Ten participants had incident EIB, eight had persistent EIB, and five remitted. Reporting more asthma-like symptoms at baseline increased the risk of incident EIB (odds ratio (OR) 2.78; 95% CI: 1.16–6.58), while FeNO, aeroallergy, and sex were not associated with incident EIB. Incident EILO occurred in three and persistent EILO in two of 27 tested. Postexercise airway responses measured by spirometry and oscillometry showed modest concordance, indicating complementary insights into airway physiology by the two methods. Elevated FeNO was associated with EIB by both spirometric (adjusted OR 2.54; 95% CI: 1.05–6.12) and oscillometric criteria (adjusted OR 3.05; 95% CI: 1.18–7.9) in nonathletes, but not in athletes. Proteomic analyses identified the chemokine CCL19 as related to reduced baseline lung function, though no systemic proteins were associated with postexercise responses.

Conclusions: Exercise-induced airway disorders like EIB and EILO are common but often overlooked in adolescent athletes. Because symptoms alone are unreliable, objective testing is essential. Differences in FeNO associations suggest distinct EIB mechanisms in athletes versus nonathletes. These results enhance understanding of exercise-related airway responses and support targeted diagnostic and management approaches. The association of CCL19 with lower baseline lung function in nonathletes also points to a possible link between immune activity and airway function in adolescents.

Keywords: Adolescents, athletes, exercise-induced bronchoconstriction, exercise-induced laryngeal obstruction, epidemiology, inflammation markers, pulmonary function testing.

Karin Ersson, Department of Medical Sciences, Akademiska sjukhuset, Uppsala University, SE-75185 Uppsala, Sweden.

ISSN 1651-6206
ISBN 978-91-513-2644-3
URN urn:nbn:se:uu:diva-568684 (http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-568684)

Grâce à toi à nouveau je respire.

J. Berg

To Tyra, Vidar & Mats

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. **Ersson K*,** Mallmin E*, Malinovschi A, Norlander K, Johansson H, Nordang L. Prevalence of exercise-induced bronchoconstriction and laryngeal obstruction in adolescent athletes. Pediatr Pulmonol. 2020;55(12):3509-16.

II. **Ersson K,** Mallmin E, Nordang L, Malinovschi A, Johansson H. A longitudinal study of exercise-induced bronchoconstriction and laryngeal obstruction in high school athletes. Scand J Med Sci Sports. 2023;33(8):1509-18.

III. **Ersson K,** Alving K, Emtner M, Janson C, Johansson H, Malinovschi A. Postexercise Airway Responses by Spirometry and Oscillometry in Nonathlete and Athlete Adolescents. Pediatr Pulmonol. 2025;60(9):e71296.

IV. **Ersson K,** Alving K, Emtner M, Janson C, Johansson H, Malinovschi A. Systemic inflammatory biomarkers in relation to lung function and exercise-induced bronchoconstriction in adolescents. Pediatric Allergy and Immunology. 2025;36(10):e70231.

*Shared first authorship.

Contents

Abbreviations

AHR	Airway hyperresponsiveness
CCL19	C-C motif chemokine 19
CCL20	C-C motif chemokine 20
CI	Confidence interval
CLE	Continuous laryngoscopy exercise
CLEC4C	C-type lectin domain family 4 member
CST5	Cystatin-D
EIB	Exercise-induced bronchoconstriction
EILO	Exercise-induced laryngeal obstruction
FDR	False discovery rate
FeNO	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in one second
FOT	Forced oscillation technique
Hz	Hertz
ICS	Inhaled corticosteroids
IgE	Immunoglobulin E
IL12B	Interleukin-12 receptor subunit beta-1
LABA	Long-acting β2-agonists
LOD	Limit of detection
LTRA	Leukotriene receptor antagonist
MASP1	Mannan-binding lectin serine protease 1
NPX	Normalized protein expression
OR	Odds ratio
Ppb	Part per billion
R_5	Resistance at 5 hertz
SABA	Short-acting β2-agonists
TNF	Tumour necrosis factor
X_5	Reactance at 5 hertz

Introduction

This thesis explores exercise-induced airway responses in adolescents, integrating epidemiological, immunological, and diagnostic perspectives. We examined adolescent athletes sampled from a national sports high school (hereinafter referred to as "athletes") as well as adolescents sampled from the general population (hereinafter referred to as "nonathletes"). Studies I and II investigated prevalence and clinical course of exercise-induced bronchoconstriction (EIB) and exercise-induced laryngeal obstruction (EILO) in adolescent athletes. Study III assessed postexercise airway responses in both adolescent athletes and nonathletes, examining links between respiratory symptoms and levels of fractional exhaled nitric oxide (FeNO), and spirometric and oscillometric pulmonary function test outcomes. Study IV investigated associations between systemic inflammation protein biomarkers and spirometric and oscillometric pulmonary function test outcomes in nonathlete adolescents —both pre- and postexercise.

This thesis provides a broad framework for understanding exercise-induced airway disorders in adolescents from multiple perspectives. By integrating epidemiological, longitudinal, physiological, and immunological approaches, the thesis contributes to the knowledge of both the clinical presentation and the underlying mechanisms. This multifaceted perspective is intended to inform improved diagnostic strategies, guide screening and follow-up practices, and contribute to promoting respiratory health in youth, ultimately facilitating participation in sports and physical activity at the desired level for young individuals.

Background

Respiratory symptoms

Regular physical exercise is widely recognized as beneficial for health and wellbeing.[1] However, in susceptible individuals exercise can trigger unpleasant respiratory sensations (exercise-induced respiratory symptoms) such as wheeze, dyspnea and chest tightness. Self-reported exercise-induced respiratory symptoms are common in adolescents and more females than males report respiratory symptoms.[2] Experiencing exercise-induced respiratory symptoms is associated with a negative impact on everyday life.[3, 4] Among athletes, exercise-induced respiratory symptoms occur even more frequently than in the general population, affecting both elite adult athletes and younger, early-career athletes.[5, 6] Similar to females in the general population, female athletes seem to report respiratory symptoms more often than their male peers.[7]

Respiratory symptoms are not confined to exercise-related contexts. Manifestations such as wheeze, cough, dyspnoea, and chest tightness are frequently observed in individuals with clinically confirmed asthma; however, these symptoms are also reported with considerable prevalence among individuals without a formal asthma diagnosis.[8, 9] Moreover, many elite athletes experience respiratory symptoms even when not engaged in exercise.[10]

Experiencing respiratory symptoms during high intensity exercise, with subsequent high ventilatory demand, can be considered physiologically normal indicating that the individual has reached the limit of their respiratory system.[11] However, nociceptive respiratory sensations during exercise may be signs of underlying pathological conditions of the airways, such as exercise-induced bronchoconstriction (EIB) or exercise-induced laryngeal obstruction (EILO).[12] These conditions are not only relevant from a health and quality of life perspective[13-15] but may, in athletes, also compromise training capacity and competitive performance.[16] Despite this, the epidemiology and mechanisms of exercise-induced airway disorders in youth remain incompletely understood, and clinical diagnostic challenges often lead to both under- and over recognition.[17, 18]

Exercise-induced bronchoconstriction

Airway hyperresponsiveness (AHR) is characterized by an exaggerated bronchoconstrictive response to a standardized bronchial challenge. Exercise-induced bronchoconstriction (EIB) constitutes a distinct clinical manifestation of AHR, precipitated by physical exertion. EIB is defined as a transient, reversible narrowing of the lower airways that occurs in response to physical exertion.[19] While EIB is frequently observed in individuals with a clinical diagnosis of asthma, it is also documented in persons without a diagnosis of asthma.[20] In elite athletic populations, the prevalence of EIB has been reported to range between 20% and 70%,[21-23] considerably higher than the prevalence estimates of 5–20% observed in the general population.[19, 24] The wide variability in reported prevalence rates among athletes can be attributed to differences in diagnostic criteria and methodology, environmental conditions, and the specific sport practiced. Endurance-based sports, particularly swimming and winter sports, are consistently associated with an elevated risk of EIB development.[23, 25] Sex-related differences in EIB prevalence remain inconclusive, as findings across studies are inconsistent, and the influence of sex on both the development and severity of EIB has yet to be thoroughly investigated.[26]

The pathogenesis of EIB remains incompletely understood. However, exercise intensity and cumulative training are considered important risk factors for EIB in athletes.[27, 28] The high ventilatory demands and prolonged hyperpnoea during training and competition impose environmental stress on the airways through heat and water loss from the lower respiratory tract, as well as exposure to airborne pollutants in some environments.[28, 29] The large volumes of inspired air during intense exercise can result in airway osmotic changes, airway inflammation, epithelial injury, and neuronal activation, all associated with EIB.[30] Presence of allergy is reported to be associated with EIB in athletes in some studies,[31, 32] but there are conflicting results with other studies reporting a majority of athletes with EIB not having allergies.[26] Two distinct phenotypes of EIB in athletes have been proposed, reflecting divergent clinical characteristics. The first phenotype is associated with classical features of asthma, including childhood onset, atopy, and AHR often demonstrated by direct bronchial challenge, i.e., methacholine provocation. The second phenotype manifests as EIB in the absence of asthma, developing during the athlete's career, characterized by AHR to indirect challenge and a lack of allergic features.[33, 34]

Identifying EIB

Self-reported exercise-induced symptoms have limited predictive value when compared to objectively confirmed EIB through bronchial challenge testing.[20] This dissociation is even more prominent in athlete populations, highlighting

that the diagnosis of EIB should not be made based on symptoms alone.[35-37] EIB based on exercise-induced symptoms may be both under- and over diagnosed in athletes considering the high prevalence of exercise-induced symptoms reported by athletes on one hand[5] and, on the other hand the high proportion of asymptomatic athletes presenting with evidence of EIB when screened.[17] Therefore, objective testing by indirect bronchial provocation and spirometry is strongly recommended.[20] Indirect challenges with exercise or surrogates for exercise: eucapnic voluntary hyperpnoea or inhalation of an osmotic agent such as mannitol or hypertonic saline triggers endogenous mediator release and subsequently causes airway smooth muscle contraction.[38] A decrease of 10-15% in forced expiratory volume in one second (FEV_1) post indirect challenge is suggested as diagnostic criteria for EIB.[38, 39] An overview of mechanism of action of indirect challenges is presented in figure 1.

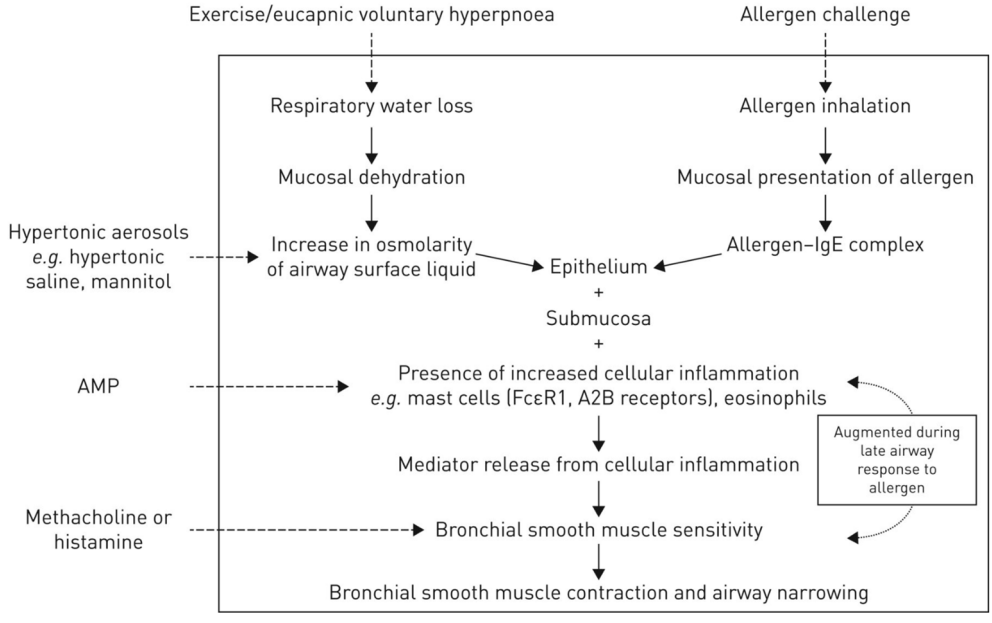

Figure 1. Mechanisms of action of indirect challenge tests. In contrast to direct challenge tests, such as those employing methacholine or histamine, which induce airway narrowing via direct stimulation and contraction of airway smooth muscle, indirect challenge tests elicit airway hyperresponsiveness through secondary pathways involving the release of endogenous mediators. Reproduced and modified from O'Byrne et al. [40] with permission from the publisher.

Detection of EIB and subsequent treatment in athletes can be crucial to reduce the potential deleterious effect on the individual's health and exercise capacity.[16, 41] A recent report indicate that also younger athletes in the beginning of their sports career have a higher prevalence of EIB compared with adolescent from the general population.[42] Screening for EIB in adolescent athletes has been suggested in some studies,[17, 43, 44] but the appropriate approach for

selection of athletes and timing of screening is unknown. Predictors of development of EIB in adolescent athletes could provide valuable information supporting clinicians in the decision making of whom and when to test for EIB.

Pulmonary function testing in the context of bronchial challenge

Dynamic spirometry is the most widely used method for assessing bronchoconstriction following bronchial challenge, assessing magnitude of change in FEV_1 from prechallenge to postchallenge measurements.[39] The technique is well established, with standardized protocols and clearly defined diagnostic thresholds,[39, 45] and it is readily available in many clinical settings. However, spirometry requires substantial patient effort to perform the manoeuvres correctly and consistently, and repeated measurements are necessary to ensure reproducibility. Given that serial assessments are typically conducted at baseline and 5-30 minutes after bronchial challenge, patient effort may decline over time, potentially affecting test reliability.[39]

The Forced Oscillation Technique (FOT), or respiratory oscillometry, is a non-invasive lung function method performed during quiet tidal breathing in which external multifrequency oscillations are applied at the mouth and the resulting pressure–flow response is analysed to determine respiratory impedance. This impedance is decomposed into resistance (Rrs), reflecting airflow opposition (airway calibre), and reactance (Xrs), reflecting elastic and inertial properties of the respiratory system.[46] As oscillometry requires less patient effort than dynamic spirometry, serial postchallenge measurements are likely to be more feasible and less influenced by patient fatigue/effort. Because oscillometry is performed during normal tidal breathing instead of the deep inspiratory manoeuvres used in dynamic spirometry, the measurements during bronchial challenge testing may be less influenced by changes in bronchial tone.[47] Oscillometry is sensitive to small-airway dysfunction and can reveal bronchodilator or challenge responses even when spirometry is preserved, but heterogeneity across devices, reference equations and interpretation thresholds remains a barrier to universal clinical adoption.[48, 49] An example of oscillometry pattern after bronchial challenge is provided in figure 2.

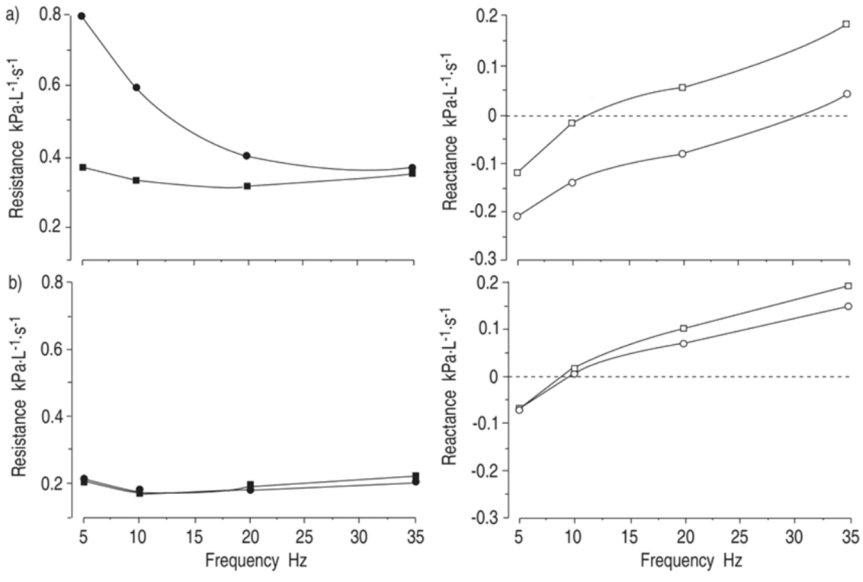

Figure 2. Example of oscillometry system data recorded pre (square) and post (dots) challenge in a) individual with positive challenge; and b) individual with negative challenge. Reproduced and modified from Schmekel *et al.*[50] with permission from the publisher.

Exercise-induced laryngeal obstruction

Exercise-induced laryngeal obstruction (EILO) refers to a narrowing of structures of the larynx during exercise, hampering airflow and limiting ventilation. The obstruction can be observed at the glottic level i.e. abnormal adduction of the vocal folds or, at the supraglottic level i.e. medial movement of the cuneiform tubercles and aryepiglottic folds decreasing the laryngeal lumen,[51] In some individuals with EILO, obstruction is present at both levels,[52] Prevalence of EILO in adolescents and young adults from the general population is estimated to be 5.7-7.5 %.[52, 53] Epidemiological studies of EILO in athletes are scarce. In one study of cross-country skiers, EILO was found in 27 %[54] and in a retrospective investigation of EILO among athletes referred to tertiary care for evaluation of exercise-induced respiratory symptoms, 35 % had EILO.[55]

The aetiology of EILO remains incompletely understood, although several potential risk factors have been proposed. These include asthma,[56] gastroesophageal reflux disease,[57] anatomical variations of the upper airway and genetic predisposition.[58] Psychological characteristics, such as a tendency toward high achievement, have occasionally been reported among individuals with EILO; however, there is no evidence to suggest an increased prevalence of psychiatric or personality disorders in cases of isolated EILO.[59] In athletic

populations, the substantial mechanical forces associated with elevated ventilatory demands, in conjunction with anatomical features—particularly the relatively smaller upper airway dimensions observed in female athletes—may contribute to the pathophysiology of EILO.[60] Taken together, the risk factors and underlying mechanisms of EILO remain insufficiently characterised, underscoring the necessity for further systematic investigation.

Identifying EILO

Exercise-induced symptoms are reported to be poor predictors also for EILO.[52, 54] Hence, objective assessment of the larynx during standardized exercise is advocated. The recommended diagnostic method for EILO is the continuous laryngoscopy exercise test (CLE), where the larynx is visualized by flexible rhinolaryngoscopy during a standardized exercise test. Laryngeal obstruction at glottic and supraglottic levels are assessed and graded at peak exercise.[51]

EILO is an important differential diagnosis to EIB. The two entities can present with similar clinical symptoms and thus be difficult to distinguish from each other without objective testing.[61, 62] Furthermore, EIB and EILO seem to coexist in some individuals,[52, 60] highlighting the need for further investigation of EILO in individuals with debilitating respiratory symptoms despite a negative EIB test or despite successful treatment of confirmed EIB.

It is important to assess if EIB or EILO is underlying, as though these conditions can have similar clinical manifestations, they require different clinical management. For EIB there are recommended strategies for pharmacological and non-pharmacological treatment,[63, 64] whereas for EILO no pharmacological treatment has been proven successful. Regarding non-pharmacological interventions for EILO the optimal approach remains unknown as randomized controlled trials are currently lacking,[60] However, for selected cases of severe EILO surgical treatment with supraglottoplasty may be successful.[65]

Course of EIB and EILO

To date, knowledge about the natural course of both EIB and EILO in athletes is limited, and longitudinal studies are scarce. There are reports of high incidence of EIB in triathletes[66] and variability of EIB in swimmers between periods with high exercise load and resting periods.[67] EILO with predominantly supraglottic obstruction has been shown to persist over time in a majority of retrospectively studied adolescents (i.e. not selected athletes) [68] as well as in endurance winter athletes.[69] Longitudinal studies of EILO with predominately glottic obstruction are lacking.

Fractional exhaled nitric oxide and EIB

Fractional exhaled nitric oxide (FeNO) is a non-invasive biomarker of airway inflammation, particularly type 2 (eosinophilic) inflammation, and is widely applied in both research and clinical practice. Standardized measurement techniques make FeNO a reproducible and practical tool for assessing asthma, monitoring anti-inflammatory treatment, and supporting diagnosis in selected cases.[70] Elevated FeNO reflects nitric oxide production in the airways, which is upregulated in response to type 2 cytokines, and is particularly pronounced in allergic asthma. Given the role of airway inflammation in EIB, several studies have investigated the utility of FeNO in this context. In asthmatic schoolchildren, FeNO has been shown to predict the occurrence of EIB, with higher FeNO values associated with increased risk of bronchoconstriction following exercise.[71] Similar findings have been observed in children at risk of asthma, where FeNO correlated with exercise challenge outcomes, although its predictive strength was limited and insufficient for use as a stand-alone diagnostic marker.[72] Among population-based studies in adolescents, findings on FeNO as a predictor of EIB have been inconsistent.[73, 74] In adult athletes the value of FeNO for predicting EIB is uncertain.[75] Overall, these findings indicate that FeNO reflects airway inflammation related to EIB susceptibility; however, its usefulness in identifying individuals at risk of EIB seems to differ between populations, highlighting the need for further studies across diverse cohorts.

Inflammation markers in plasma in relation to lung function and EIB

Inflammation is very likely to be a central determinant of lung function development and long-term trajectories, with both systemic and airway-specific processes contributing to pathological outcomes,[76] In persistent childhood asthma, chronic type 2 inflammation, reflected by elevated blood eosinophil counts, has consistently been associated with impaired lung growth and an accelerated decline in pulmonary function.[77, 78] This inflammatory burden is believed to alter airway remodeling processes during critical windows of lung growth, increasing the risk of fixed airflow obstruction and irreversible functional impairment later in life.[77]

AHR reflects both structural changes in airway smooth muscle and heightened inflammatory signaling.[79] Longitudinal studies suggest that adolescents with concomitant eosinophilic inflammation and AHR are particularly prone to abnormal lung function trajectories, characterized by reduced peak lung function attainment and early decline.[80, 81] Mechanistically, this may involve synergistic effects of Th2-driven cytokines, which enhance eosinophil recruitment, immunoglobulin E (IgE) production, and airway hyperreactivity, thereby perpetuating a cycle of inflammation and remodeling.[80]

These findings point toward the existence of a high-risk inflammatory phenotype in adolescence that drives disease progression into adulthood. Understanding the interplay between complex inflammatory pathways, airway remodelling, and lung function development is therefore essential, as it can enable the early identification of individuals most at risk for long-term impairment and inform the development of targeted interventions aimed at modifying disease course and preserving lung health.

Atopy in relation to lung function and AHR

Atopy, defined as a genetic predisposition to develop IgE-mediated allergic responses, has been consistently linked with altered lung function and AHR.[82] Atopy is diagnosed through clinical history supported by objective tests. The most common methods are skin prick testing (SPT) and serum allergen-specific IgE measurement.[83, 84] Population-based studies have shown that atopic individuals often demonstrate heightened AHR to direct stimuli such as histamine, even in the absence of overt asthma symptoms.[85] Environmental exposures play a key role, as allergen contact has been associated with increased prevalence and severity of AHR among school-aged children.[86] Similarly, investigations in both children and adolescents indicate that atopy is a significant determinant of AHR in the general population.[87] Longitudinal cohort research has further confirmed that allergy skin test reactivity correlates not only with increased AHR but also with reduced lung function, respiratory symptoms, and asthma diagnoses during adolescence.[88] Complementary evidence demonstrates that atopic children show lower baseline lung function and greater airway responsiveness than their non-atopic peers, emphasizing the developmental impact of atopy on respiratory health.[89] In addition, EIB has been shown to be more frequent and severe in allergic children, underscoring the clinical relevance of the link between atopy, lung function, and airway reactivy.[90] Longitudinal data suggest that AHR tends to decline from childhood into adulthood, whereas atopic sensitization often increases with age, underscoring the dynamic and multifactorial nature of their relationship.[91] Collectively, these findings highlight atopy as an important risk factor underlying the development of airway hyperresponsiveness and impaired lung function.

Swedish sports high school

In Sweden, many adolescents combine high school education with pursuing an athlete career through attendance at special sports high schools. The Swedish sports high school education are divided into three different levels; National Sports High School with national recruitment of students (*Riksidrottsgymnasium, RIG*), Nationally Approved Sports Education with regional

recruitment of students (*nationellt godkänd idrottsutbildning, NIU*) and Locally Approved Sports Education with regional and local recruitment of students (*lokalt godkänd idrottsutbildning, LIU*). In RIG and NIU, the students have curricular sports education of their specific sport discipline daily and in LIU generally two times per week. In addition to the curricular sports activities the vast majority of the students also do extracurricular training and competing within a local or national sports association. Celsiusskolan in Uppsala is the largest sports high school in Sweden recruiting approximately 300 students each year offering sports high school education in 23 different sports disciplines.

Aim of the thesis

The overall aims of this doctoral project were to investigate exercise-induced airway responses in adolescents by integrating epidemiological, clinical, immunological, and diagnostic perspectives. The project primarily focused on the prevalence and clinical course of EIB and EILO in athletes; to examine the relationships between respiratory symptoms, exhaled nitric oxide, and EIB in both athletes and nonathletes; and to explore associations between systemic inflammation biomarkers, lung function, and EIB in nonathletes.

The specific aims were:

I. To determine the prevalence of EIB and EILO in adolescent athletes using standardized objective testing, and to evaluate the relationship between self-reported symptoms and objective outcomes.

II. To examine the longitudinal course of EIB and EILO over a two-year period in athletes, and to identify baseline characteristics associated with incident EIB.

III. To assess postexercise airway responses in adolescent athletes and nonathletes using spirometry and oscillometry, and to examine whether self-reported respiratory symptoms and FeNO levels are associated with airway changes in these groups.

IV. To explore associations between systemic inflammation proteins, atopy, lung function, and EIB in order to identify potential immunological correlates of lung function and EIB in adolescents.

Methods

Ethics

Written informed consent was obtained from all participants upon enrolment in the study. For individuals younger than 15 years of age, informed consent was additionally collected from their legal guardians. Ethical approval for the studies was granted by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2011/413 and Dnr 2016/169).

Material and methods

Study designs and description of data types in included papers are presented in table 1.

Table 1. Overview of study design, study populations and collected data in included papers.

Paper	Study design	Study population	Data types	Data levels
I	Cross-sectional, stratified by self-reported exercise-induced dyspnea	CELADY: Athletes, Uppsala, Sweden , 2016-2017 Random sample (n=98) tested	Questionnaire Physiological tests (EIB test, CLE test)	Questionnaire: categorical/ordinal EIB: categorical (EIB positive/negative); CLE: categorical (EILO positive/negative)
II	Longitudinal (baseline 2016–17, follow-up 2018–19)	CELADY: Athletes (n=58 EIB tested, n=27 CLE-tested at baseline and follow-up)	Questionnaire Physiological tests (EIB test, CLE test) Biomarker (FeNO)	Questionnaire: categorical/ordinal; EIB: continuous (ΔFEV_1), categorical (EIB positive/negative) CLE: categorical (EILO positive/negative) FeNO: continuous
III	Cross-sectional comparison (athletes vs nonathletes)	CELADY: Athletes (n=98) ANDAS: Nonathletes (n=143)	Questionnaire Physiological tests (EIB test) Biomarker (FeNO)	Questionnaire: categorical/ordinal; EIB: continuous ($\Delta FEV_1, \Delta R_5, \Delta X_5$), categorical (EIB positive/negative by FEV_1 or R_5) FeNO: continuous, categorical (elevated FeNO)
IV	Cross-sectional, biomarker profiling study	ANDAS: Nonathletes (n=143)	Questionnaire Physiological tests (Baseline lung function, EIB test) Biomarkers (IgE, proteomics)	Questionnaire: categorical/ordinal Lung function: continuous (FEV_1%, R_5 z-score, X_5 z-score) EIB: continuous ($\Delta FEV_1, \Delta R_5, \Delta X_5$), categorical (EIB positive/negative by FEV_1) IgE: categorical (atopy yes/no) Proteomics: continuous (NPX values)

EIB, exercise-induced bronchoconstriction; FEV_1, forced expiratory volume in one second; EILO, exercise-induced laryngeal obstruction; CLE test, continuous laryngoscopy exercise test; FeNO, fractional exhaled nitric oxide; R_5, respiratory resistance at 5 Hz; X_5, respiratory reactance at 5 Hz; IgE, immunoglobulin E; NPX, normalized protein expression

Study populations

Athletes, the CELADY-study (study I-III)

In 2016 and 2017, all first-year students at the sports high school at Celsiusskolan in Uppsala, Sweden were invited to participate in the study (n=549). After informed written consent, the participants answered a questionnaire about respiratory symptoms, asthma and allergy. The questionnaire included a critical item on whether the participant had experienced exercise-induced dyspnea within the past 12 months. The participants were stratified in two groups by self-reported exercise-induced dyspnea: dyspnea and nondyspnea.

A random sample from each stratum were invited to two clinical visits; visit one for FeNO measurements and an EIB test and visit two for a CLE test (baseline). In 2018 and 2019, during their third year in sports high school, the participants were once again invited to answer the questionnaire and repeat the visits for EIB test and CLE test (follow-up). Data collection (questionnaires and objective tests) at both baseline and follow-up were done in the corresponding time period of each year, i.e., September-November.

Nonathletes, the ANDAS-study (study III-IV)

Participants were recruited from a population-based study designed to investigate the prevalence of EIB among adolescents aged 13–15 years. In total, 2,309 adolescents completed a questionnaire about respiratory symptoms, asthma and allergy. The participants were stratified in two group by self-reported exercise-induced dyspnea: dyspnea and nondyspnea.

Following stratification, 150 adolescents were randomly selected and invited to attend two clinical study visits. At the first visit, anthropometric data (including height, weight, and body mass index) were recorded, and information on current and past asthma medication use was collected. In addition, FeNO was measured and venous blood samples were obtained for laboratory analyses, including assessments of immunoglobulin E (IgE) sensitization and plasma protein measurements. At the second visit the participants performed an EIB test.

Data collection

Questionnaire variables

The following items in the questionnaire were used to measure the study variables:

Exercise-induced dyspnea: "Have you had an attack of shortness of breath that happened during or after strenuous activity at any time during the last 12 months?" [92]

Wheeze: "Have you had wheezing or whistling in your chest at any time in the last 12 months?" [93]

Waking up with chest tightness: "Have you been woken up with a feeling of tightness in your chest at any time in the last 12 months?" [93]

Daytime dyspnea: "Have you had an attack of shortness of breath that came on during the day when you were at rest at any time in the last 12 months?" [92]

Nocturnal dyspnea: "Have you been woken by an attack of shortness of breath at any time in the last months?" [93]

Physician diagnosed asthma: Have you ever been diagnosed with asthma by a physician?

Medication: Have you in the last three months used the following medications: inhaled corticosteroids, long-acting β2-agonists, inhaled corticosteroids in combination with long-acting β2-agonists, short-acting β2-agonists, leukotriene receptor antagonists?

Exercise-induced respiratory symptoms: "In the last 12 months have you, more than once, had one or several of the following symptoms during or directly after exercise: wheeze or whistling in your chest, tightness in your chest, an attack of shortness of breath, cough, tightness in your throat, choking sensation, hoarseness, and noise during inspiration?" [94]

Self-reported aeroallergy: "When in contact with furry animals or pollen, do you ever experience one or more of the following: cough, shortness of breath, wheeze, tightness in your chest, sneezing, blocked or runny nose, and irritated or watery eyes?"

Asthma-like symptoms: were defined from the questions wheeze, waking up with chest tightness, daytime dyspnea, nocturnal dyspnea. [93]

Current asthma was defined as a physician-diagnosed asthma at any time, combined with the presence of respiratory symptoms within the past 12 months and/or the use of asthma medication within the past 3 months.

Weekly training hours (study I-II) was defined from the question "How many hours on average do you spend training and competing in a normal week?"

Physiological and biomarker variables

Baseline FOT measurements were performed with the Resmon Pro Full device (Restech Srl), which applies multifrequency oscillatory signals (5, 11, and 19 Hz) to assess respiratory mechanics. Participant performed the measurement sitting in an upright position supporting their cheeks with their hands and with a nose clip in place, in accordance with recommendations.[49] Each measurement was repeated in duplicate to ensure reliability. Baseline respiratory resistance at 5 Hz (R_5) and respiratory reactance at 5 Hz (X_5) were determined by calculating the mean of two technically acceptable trials, each consisting of at least 10 acceptable breaths.

Baseline spirometry was performed using the CardioPerfect dynamic spirometer (Welch Allyn) and conducted according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[95] Participant performed the maneuvers sitting in a chair with a nose clip in place. Forced expiratory volume in one second (FEV_1) was recorded as the highest value obtained from three acceptable and reproducible maneuvers, where reproducibility was defined as the two highest FEV_1 values differing by no more than 150 mL.

FeNO (study II-III) was measured prior to the EIB test (for athletes: as first measurement at clinical visit for EIB test, for nonathletes: at first clinical visit). Measurements were performed at 50 mL/s in accordance with ATS/ERS recommendations[70] (for athletes: NIOX Vero, Circassia, for nonathletes: NIOX Flex, Aerocrine). Athletes were instructed to avoid physical exercise, caffein, nicotine and heavy meals within 4 hours of the test. Nonathletes were instructed to avoid nitrate-rich food and physical exercise on the morning of the day of the test.

Elevated FeNO (study III) was defined as FeNO $\geq$ 25 parts per billion (ppb).

Atopy (study IV) was defined by measuring IgE antibodies against a mixture of common aeroallergens, including mite, furry animal, mould, grass, tree, and weed pollen (Phadiatop; ImmunoCAP; Thermo Fisher Scientific). Participants with IgE levels $\geq$0.1 kUA/L were classified as atopic.

Proteomics (study IV)

Two high-throughput multiplex immunoassays were utilized for proteomics analyses, each quantifying 92 protein biomarkers simultaneously. The proteins were preselected by the manufacturer in two standard panels: the Olink Target 96 Inflammation panel and the Immune Response panel (SciLifeLab).[96] Four proteins were present in both panels; these were included only from the Inflammation panel to avoid duplication.

Of the 180 proteins measured, 45 (19 from the Inflammation panel and 26 from the Immune Response panel) had more than 25% of samples below the limit of detection (LOD) and were therefore excluded from further analyses. For the remaining 135 proteins, actual values below the LOD were retained in the analyses. Protein levels are expressed as $\log_2$-transformed normalized protein expression (NPX) units, representing relative quantification.

Exercise-induced bronchoconstriction test (study I-IV)

Prior to testing, participants received standardized instructions to minimize potential confounding factors that could influence airway reactivity. They were asked to refrain from engaging in vigorous physical activity, consuming caffeine, nicotine, or heavy meals within the four hours preceding the test. In addition, to reduce pharmacological influences on airway measurements, participants were instructed to withhold specific respiratory medications: short-acting β2-agonists for at least 8 hours before the test, long-acting β2-agonists for 24 hours, leukotriene receptor antagonists for 72 hours, and inhaled corticosteroids on the day of testing.

Baseline assessments of lung function were carried out preexercise using FOT and spirometry as described above. The exercise challenge was conducted on a treadmill, with participants wearing a nose clip to prevent nasal breathing and inhaling dry, room-temperature air (H_2O content < 5 mg/L, 18–22°C) through a tubing system connected to a central gas supply. The exercise protocol lasted 7–8 minutes in total. Heart rate was monitored continuously to ensure that participants reached 90% of their predicted maximum heart rate—calculated as $(220 - \text{age}^{97}) \times 0.9$—within the first two minutes of exercise. Participants were then required to sustain this target heart rate for an additional 5–6 minutes to provide an adequate bronchoprovocative stimulus.

Postexercise lung function was reassessed at multiple time points to capture both immediate and delayed airway responses. FOT was performed as a single measurement consisting of at least five artefact-free breaths, while spirometry was performed in duplicate. FOT was performed before spirometry at each time point. These measurements were repeated at 5, 10, 15, 30 and 60 minutes after the cessation of exercise (in study III and IV measurements 5-30 minutes postexercise were used). An overview of the protocol for the EIB test is

presented in figure 3. EIB was defined as an increase in R_5 of at least 25% from baseline[98] or a decrease in FEV_1 of 10% or more relative to baseline measurements at any postexercise time point[39].

All exercise challenge tests were supervised by investigators (respiratory physiotherapists), who were blinded to participants' questionnaire data to minimize observer bias. This ensured that lung function assessments and EIB classification were performed independently of participants' self-reported symptoms or history.

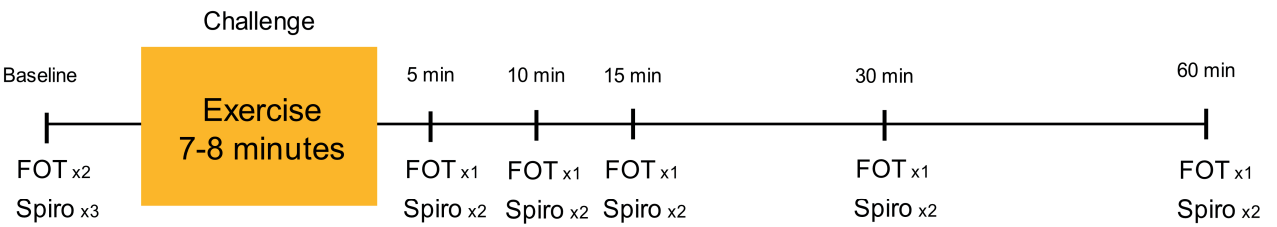

Figure 3. Overview of protocol for the EIB test. For study III-IV measurements 5-30 minutes post-exercise were used.

FOT, forced oscillation technique; Spiro, spirometry

Continuous laryngoscopy exercise test (study I-II)

The CLE tests were performed 3-51 (median 12) days after the EIB tests. Prior to the CLE test the participants were instructed to continue any prescribed asthma therapy, including inhaled bronchodilators as premedication before the test when applicable.

The CLE tests were performed using bicycle ergometry (Monark model 828E; Monark Exercise AB, Vansbro, Sweden). The bicycle seat was adjusted for each participant. Naphazoline-lidocaine was sprayed into the nostrils for local anesthetic and decongestive effect in the nasal cavity. A rhinolaryngoscope (Olympus ENF-P3; Olympus Europa SE & Co. KG, Hamburg, Germany) was inserted in one nostril. To provide a detailed view of the larynx throughout the test, the tip of the rhinolaryngoscope was placed just above the epiglottis and the rhinolaryngoscope was then fixed to the nose and fastened to a helmet, worn by the participant, and connected to a camera (Ubicam; Comeg Medical, La Ciotat, France). Normal adduction and abduction ability of the vocal folds was confirmed.

Participants were instructed to pedal with a frequency of 80 rotations per minute and continue until experiencing disabling shortness of breath or until complete exhaustion. The load started at 80 watts and was increased by 40 watts every second minute until end of test. The participants were instructed to exercise until exhaustion. Heart rate was monitored continuously and the protocol required the participant to reach >90% of their predicted maximum heart rate—calculated as $(220 - \text{age}^{97}) \times 0.9$. The larynx was filmed during the entire test and continuously for two minutes after exercise cessation. Laryngeal obstruction at glottic and supraglottic levels was graded 0-3 in accordance with the criteria described by Maat *et al.*[99] A positive CLE test, consistent with EILO, was defined as obstruction of grade two or higher at the glottic and/or the supraglottic level. The obstruction was graded during the test by the attending investigator. In uncertain cases or in cases graded as obstruction level two or higher, the recordings from the tests were graded by one additional investigator. All CLE investigators were physicians specialized in otorhinolaryngology.

Statistical methods

Across the four studies, statistical analyses were conducted using STATA (versions 14.2–16.1) and, in addition for study I SAS 9.4 was used. Normality of continuous variables was evaluated using the Shapiro–Wilk test. Normally distributed variables were summarized as means with standard deviations (SD), while non-normal data were presented as medians with interquartile ranges (Q1–Q3) or geometric means with 95% confidence intervals (CI). Group comparisons for continuous variables were performed using unpaired Student's

t-tests, one-way ANOVA with Tukey's post-hoc test, or Kruskal–Wallis tests, depending on data distribution. Categorical variables were analyzed using chi-square or Fisher's exact tests.

Estimated prevalences were calculated based on four strata: dyspnea females, dyspnea males, nondyspnea females, and nondyspnea males. The prevalence rates of EIB and EILO were estimated by multiplying the proportions of positive tests within the strata with their relative proportion of the study population. Wald based confidence limits were calculated for estimates >25% and modified Clopper–Pearson confidence limits were calculated for estimates <25%.

Associations between exposures (sex, FeNO, plasma proteins, asthma-like symptoms) and outcomes (EIB, EILO, lung function, postexercise airway responses) were assessed using logistic and linear regression models, adjusted for relevant covariates such as sex and height. Correlations between continuous variables were examined with Spearman's rank coefficients. Statistical significance was defined as $p < 0.05$ throughout. To address multiple comparisons, the Benjamini–Hochberg false discovery rate (FDR) correction was applied at 0.05 in study IV. An overview of exposures, covariates and outcomes as well as statistical methods used in the included papers is presented in table 2.

Table 2. Overview of exposures, covariates, outcomes and statistical methods in included papers.

Paper	Exposures and covariates	Outcomes	Statistical methods
I	Exercise-induced dyspnea Sex	EIB: EIB test (spirometry): $\Delta FEV_1 \leq -10\%$ EILO: CLE test, laryngeal obstruction grade ≥2 at glottic/supraglottic level	T-test Chi-square or Fisher's exact test Weighted prevalence estimates by sex strata Confidence intervals: Wald (>25%) or modified Clopper–Pearson (<25%)
II	Asthma-like symptoms Exercise-induced respiratory symptoms Aeroallergy FeNO Sex	EIB: incident, persistent, remission EILO: incident, persistent, remission	Shapiro–Wilks for normality ANOVA/Kruskal–Wallis with Tukey post-hoc Fisher's test for categorical data Logistic regression (OR, 95% CI) Significance at $p<0.05$
III	FeNO Elevated FeNO Wheeze Exercise-induced dyspnea Sex Height	EIB (spirometry): $\Delta FEV_1 \leq -10\%$ EIB (FOT): $\Delta R_5 \geq 25\%$ Post-exercise airway responses: ΔFEV_1 ΔR_5 ΔX_5	Shapiro–Wilks for normality Spearman's rank correlations Logistic regression (OR, 95% CI) Linear regression (β, 95% CI) Significance at $p<0.05$
IV	Plasma protein levels Atopy Sex	Baseline lung function: FEV_1 % predicted R_5 z-score X_5 z-score Post-exercise airway responses: ΔFEV_1 ΔR_5 ΔX_5	Shapiro–Wilks for normality Linear regression (β, 95% CI) Multiple testing correction: FDR (Benjamini–Hochberg, q=0.05)

EIB, exercise-induced bronchoconstriction; FEV_1, forced expiratory volume in one second; EILO, exercise-induced laryngeal obstruction; CLE test, continuous laryngoscopy exercise test; FeNO, fractional exhaled nitric oxide; OR, odds ratio; CI, confidence interval; FOT, forced oscillation technique; R_5, respiratory resistance at 5 Hz; X_5, respiratory reactance at 5 Hz; FDR, false discovery rate

Artificial Intelligence in thesis

This thesis was partially created with the assistance of two large-scale language generation models: Open AI GPT-5 and Microsoft Copilot. Upon generating draft language, I reviewed, edited, and refined the text to my own liking and retain full responsibility for the content presented in this publication.

Results

Paper I

In this cross-sectional investigation of 367 first-year students enrolled at a Swedish sports high school, standardized diagnostic testing was used to determine the prevalence of EIB and EILO. A total of 98 adolescents underwent an exercise challenge to evaluate EIB, and 75 of them completed an additional CLE test to investigate EILO. Among the participants, 8 of 41 in the dyspnea group and 16 of 57 in the nondyspnea group had a positive EIB test. Correspondingly, positive CLE tests were found in 5 of 34 and 3 of 41 adolescents, respectively. Characteristics of participants who underwent EIB tests are presented in table 3.

Table 3. Characteristics of participants who underwent EIB tests.

	All tested (n=98)	Dyspnea (n=41)	Nondyspnea (n=57)	*p-value*
Age (years), mean (SD)	15.8 (± 0.1)	16 (±0.2)	15.8 (±0.1)	>0.99
Females, n (%)	57 (58.2)	29 (70.7)	28 (49.1)	0.053
Weekly training hours, median	12.5	12.5	12.5	>0.99
BMI, mean (SD)	22.1 (±6.0)	21.1 (±6.0)	22.2 (±6.1)	0.52
Overweight and obesity[a] (%)	18 (19.4)	7 (18.4)	11 (20)	0.85
FEV_1 % predicted[b], mean (SD)	95.8 (±9.9)	97.5 (±10.8)	94.6 (±9.2)	0.92
Current asthma[c], n (%)	21 (21.4)	18 (43.9)	3 (5.2)	<0.001
Rhinitis, n (%)	26 (27.6)	13 (33.3)	13 (23.6)	0.30
Wheeze, n (%)	34 (35.4)	21 (52.5)	13 (23.6)	0.002
Day time Dyspnea, n (%)	11 (11.2)	6 (15)	5 (8.6)	0.34
Nocturnal Dyspnea, n (%)	2 (2)	0	2 (3.4)	0.51

ICS[d], n (%)	13 (13.5)	9 (23.1)	4 (7.1)	0.035
SABA[d], n (%)	28 (29.2)	18 (46.2)	10 (17.5)	0.002
LABA[d], n (%)	4 (4.3)	2 (5.4)	2 (3.6)	>0.99
LTRA[d], n (%)	1 (1.1)	0 (0)	1 (1.8)	>0.99
Exercise tests, positive/all tested, n (%)				
EIB test	24/98 (24.5)	8/41 (19.5)	16/57 (28.1)	0.46
CLE test	8/75 (10.7)	5/34 (14.7)	3/41 (7.3)	0.46

P-value: Dyspnea versus Non-dyspnea. BMI, body mass index (kg/m^2); ICS, inhaled corticosteroids; SABA, short-acting β2-agonists; LABA, long-acting β2-agonists; LTRA, leukotriene receptor antagonist; EIB test, exercise-induced bronchoconstriction test; CLE test, continuous laryngoscopy exercise test

[a] Overweight and obesity defined as BMI ≥ 85th percentile,

[b] Refolded before exercise-induced bronchoconstriction test,

[c] Self-reported physician-diagnosed with symptoms and/or medication excluding SABA only,

[d] Any use in last three months

Available data: all 98 subjects responded to all the questions in the questionnaire except wheeze, ICS and SABA n = 96, rhinitis n = 94, BMI, overweight and obesity, LABA and LTRA n = 93.

The estimated prevalence of EIB in the entire cohort was 23.1% (95 % confidence interval (CI) 14.5–33.8), while EILO was observed in 8.1% (95 % CI 2.5–18.5). There were no statistically significant differences in the prevalence of EIB or EILO between those who reported exercise-induced dyspnea and those who did not, suggesting that self-reported breathing difficulty is a weak indicator of underlying airway pathology**.** The study also demonstrated that EIB and EILO occasionally coexisted in the same individuals, highlighting that EIB and EILO can overlap yet represent distinct physiological mechanisms**.** EIB was considerably more common than EILO in this population.

Paper II

The second study followed the sports high-school cohort over a two-year period to examine the natural course of EIB and EILO and to identify baseline factors related to incident EIB. Fifty-eight adolescents participated in both baseline and follow-up testing, with 27 of them undergoing CLE testing at both time points. Among these participants, ten developed new-onset EIB (incident EIB), eight exhibited persistent EIB across both measurements, five were classified as EIB at baseline but not at follow-up, and 35 remained negative at both assessments. Thus, approximately two in nine adolescents developed new EIB over two years, indicating that the condition can arise during mid- to late adolescence even among previously unaffected individuals.

Incident EIB was significantly associated with asthma-like symptoms at baseline, particularly waking up with chest tightness (odds ratio (OR) 4.38; 95 % CI 1.06–22.1). Each additional reported asthma-like symptom increased the odds of developing EIB by nearly threefold (OR 2.78; 95 % CI 1.16–6.58). In contrast, no significant relationships were observed between the emergence of EIB and FeNO levels, self-reported aeroallergy, exercise-induced symptoms, or sex. Results from analyses of associations between asthma-like symptoms and exercise-induced symptom, and incident EIB are presented in table 4.

Table 4. Logistic regression analyses of associations of asthma-like symptoms and exercise-induced symptoms at baseline and incident EIB at follow-up. EIB-negative n=35, incident EIB n=10.

	Participants, n (%)	OR	95% CI
Asthma-like symptoms:			
Wheeze	12 (27)	2.25	0.50, 9.99
Waking up with chest tightness	11 (24)	4.83	1.06, 22.09
Shortness of breath during daytime rest†	4 (9)	13.36	0.92, 786.34
Waking up with shortness of breath	0	-	
Numbers of asthma-like symptoms, continuous		2.78	1.16, 6.58
Asthma-like symptoms, categorical†			
0 symptoms (ref)	26 (58)	1.00	
1 symptom	13 (29)	3.29	0.46, 27.20
≥2 symptoms	6 (13)	6.99	0.65, 84.58
Exercise-induced symptoms:			
Wheeze	16 (36)	1.28	0.31, 5.42
Chest tightness	15 (33)	0.17	0.02, 1.47
Shortness of breath	20 (46)	2.14	0.51, 9.02
Cough	21 (47)	1.90	0.45, 7.98
Throat tightness	20 (46)	1.67	0.38, 7.29
Choking sensation†	8 (18)	1.20	0.10, 8.66
Hoarseness	13 (29)	2.31	0.51, 10.54
Noise during inspiration	17 (38)	0.64	0.14, 2.92
Numbers of exercise-induced symptoms, continuous		1.03	0.79, 1.35
Exercise-induced symptoms, categorical†			
0 symptoms (ref)	11 (24)	1.00	
1–2 symptoms	14 (31)	0.46	0.03, 4.99
3–4 symptoms	7 (16)	1.06	0.07, 13.25
≥5 symptoms	13 (29)	0.80	0.08, 7.78

† Analysis performed with exact logistic regression

EIB, exercise-induced bronchoconstriction; OR, odds ratio; 95% CI, 95% confidence interval. Confidence intervals not containing 1 are considered significant.
Analyses made by logistic regression models or exact logistic regression models with each asthma-like symptom (exposure) and incident EIB (outcome), sum of asthma-like symptoms as a continuous variable (exposure) and incident EIB (outcome) and asthma-like symptoms as categorical variable (exposure) and incident EIB. The same methods were used for exercise-induced symptoms and incident EIB (outcome).

Regarding laryngeal obstruction, incident EILO occurred in three and persistent EILO in two of the 27 athletes who underwent repeated CLE testing, underscoring that this condition also may persist or develop over time. Results from CLE tests at baseline and follow-up are presented in table 5. These longitudinal data demonstrate that both EIB and EILO are dynamic conditions in adolescence, not fixed traits, and may require repeated evaluation as athletes mature and training load increases.

Table 5. Results of CLE tests at baseline and follow-up.

	CLE test baseline	CLE test follow-up
Participants, n	75	27
Female, n (%)	49 (65)	19 (66)
EILO, n (%)	8 (11)	5 (19)
Incident EILO, follow-up, n	-	3
Glottic, n	2	0
Supraglottic, n	4	5
Both glottic and supraglottic, n	2	0

CLE, continuous laryngoscopy exercise; EILO, exercise-induced laryngeal obstruction.

Paper III

The third study compared postexercise airway responses in 241 adolescents, including 98 athletes and 143 nonathletes, using both spirometry and oscillometry. The objective was to evaluate whether FeNO and respiratory symptoms were associated with postexercise airway responses and to determine whether oscillometry added diagnostic value beyond spirometry. Characteristics of participants per group are presented in table 6.

Table 6. Baseline characteristics of the participants presented per group.

	Athletes (n=98)	Nonathletes (n=143)
Female, n (%)	57 (58.2)	86 (62.1)
Age (years), median (Q1-Q3)	16 (15-16)	14 (14-15)
Height (cm), median (Q1-Q3)	172 (167-180)	168 (163-175)
BMI to age[a], n (%) Overweight > +1 SD Normal -2SD - +1SD Thinness < -2 SD	 24 (24.5) 73 (74.5) 1 (1)	 29 (20.2) 108 (75.5) 6 (4.2)
Rhinitis, n (%)	26 (27.6)	48 (33.6)
Current asthma[b], n (%)	21 (21.4)	43 (30.1)
Wheeze[c], n (%)	34 (34.7)	56 (39.2)
Exercise-induced dyspnea[c], n (%)	41 (41.8)	97 (67.8)
ICS[d], n (%)	11 (11.8)	23 (16.1)
FeNO (ppb), geometric mean (95% CI)	16.2 (14.7, 17.9)	14.5 (13.0, 16.2)
Elevated FeNO (≥25 ppb), n (%)	20 (20.4)	26 (18.2)
FEV_1 % predicted[e], mean (SD)	95.8 (±10)	92.5 (±10.2)
Abnormal FEV_1/FVC ratio[f], n (%)	3 (3)	10 (6.9)
R_5 (cmH20*s/L), mean (SD)	2.92 (±0.72)	3.83 (±0.76)
Abnormal R_5[g], n (%)	2 (2)	20 (14)
X_5 (cmH20*s/L), mean (SD)	-0.69 (±0.25)	-1.09 (±0.44)
Abnormal X_5[h]	2 (2)	10 (6.9)

Abbreviations: Q1, first quartile; Q3, third quartile; SD, standard deviation; BMI, body mass index; ICS, inhaled corticosteroid; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; 95% CI, 95% confidence interval; FEV_1, forced expiratory volume in one second; R_5, respiratory resistance at 5 Hz; X_5, respiratory reactance at 5 Hz

Available data: All 143 participants responded to all the questions except athletes regarding ICS (N=93).

[a] Cut-offs according to World Health Organization

[b] Self-reported physician-diagnosed with symptoms and/or medication

[c] Self-reported symptom in the preceding 12 months

[d] Any use in the preceding 3 months
[e] Reference value: Global Lung Initiative
[f] < Lower limit of normal according to Global Lung Initiative
[g] > Upper limit of normal according to the reference equation by Ducharme
[h] < Lower limit of normal according to the reference equation by Ducharme

Following standardized treadmill exercise testing, EIB was identified in 70 participants using spirometry (≥ 10 % fall in FEV_1) and in 81 participants using oscillometry (≥ 25 % increase in R_5), while 37 were positive by both methods. Thus, oscillometry detected additional cases not captured by spirometry alone. Proportions of participants who were EIB positive by FEV_1, R_5 or both methods are presented per group in figure 4.

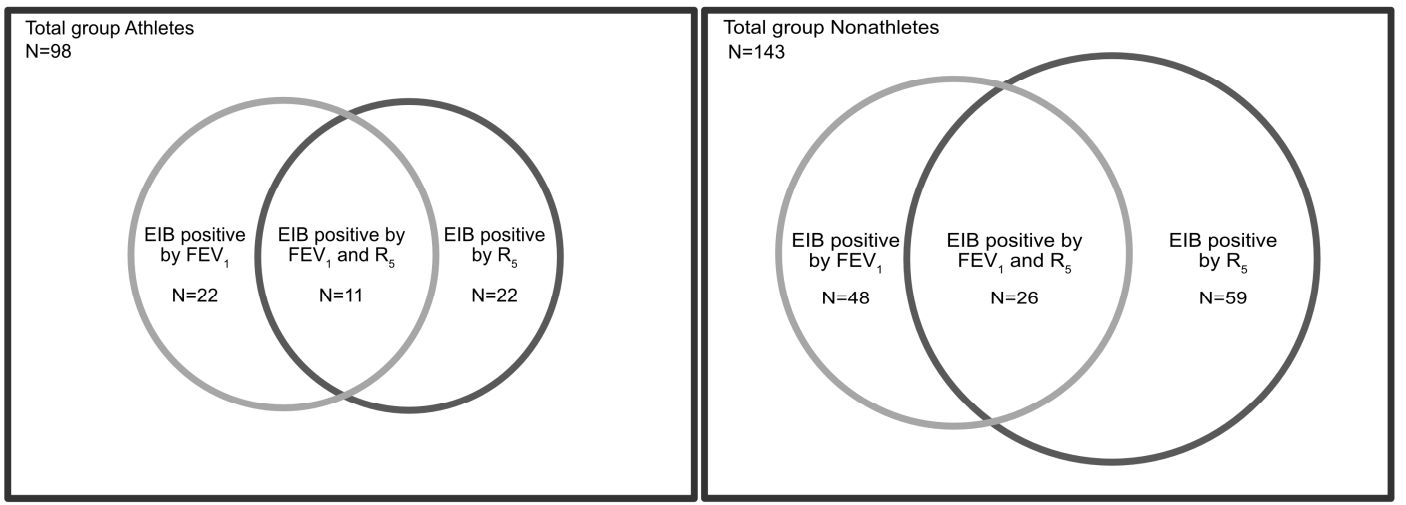

Figure 4. Proportion of participants being EIB positive by FEV_1, R_5 or both methods presented per group.

EIB, exercise-induced bronchoconstriction; FEV_1, forced expiratory volume in one second; R_5, respiratory resistance at 5 Hz

Among nonathletes, FeNO showed significant correlations with postexercise changes in lung function (ΔFEV_1 r_s −0.17, p 0.04; ΔR_5 r_s 0.35, $p < 0.001$; ΔX_5 r_s −0.25, p 0.005). Elevated FeNO (≥ 25 ppb) increased the odds of EIB both when defined by spirometry (adjusted OR 2.54, 95 % CI 1.05–6.12) and by oscillometry (adjusted OR 3.05, 95 % CI 1.18–7.90). In contrast, no such associations were observed among athletes, suggesting a more complex or multifactorial airway physiology in this group, possibly due to repeated exposure of the airway to environmental triggers or training load. Moreover, in nonathletes, self-reported respiratory symptoms were significantly related to measured airway responses, while these relationships were again absent in athletes.

Paper IV

The fourth study explored potential systemic inflammatory correlates of lung function and EIB using multiplex plasma proteomics in nonathletes (143 adolescents aged 13–15 years). Lung function was assessed with spirometry and oscillometry before and after an exercise challenge, and 180 inflammatory and immune response-related plasma proteins were quantified using Olink proximity extension assays (Olink Target 96 Inflammation and Target 96 Immune response). After quality control, 135 proteins were included in statistical analyses.

Linear regression analyses, corrected for multiple testing, identified the chemokine CCL19 as the only protein significantly associated with both lower baseline FEV_1 % predicted and lower X_5 z-scores, indicating impaired lung function and small-airway mechanics. Results from the analyses of plasma protein levels and baseline lung function measurements are shown in table 7 for all proteins that exhibited significant associations before correction for multiple testing, presented separately for each lung function outcome.

Table 7. Associations between levels of plasma proteins and baseline lung function measurements analysed by linear regression models and presented per outcome. For FEV_1% crude models were used and for R_5 z-score and X_5 z-scores the models were adjusted for sex. q-values were derived by Benjamin Hochberg correction with false discovery rate 0.05. All proteins with significant associations for each outcome before BH correction are included in the table.

		Estimates	95% CI	q-value
FEV_1 %				
CCL19	C-C motif chemokine 19	-4.96	(-7.57, -2.35)	0.037
LIFR	Leukemia inhibitory factor receptor	-9.95	(-18.18, -1.73)	0.952
CD8A	T-cell surface glycoprotein CD8 alpha chain	3.61	(0.47, 6.75)	0.952
IFNLR1	Interferon lambda receptor 1	-5.22	(-9.99, -0.45)	0.952
IL17C	Interleukin-17C	2.44	(0,17, 4.71)	0.952
CNTNAP2	Contactin-associated protein-like 2	-3.95	(-7.84, -0.06)	0.952
R_5 z-score				
TNF	Tumour necrosis factor	0.64	(0.29, 0.98)	0.054
CCL19	C-C motif chemokine 19	0.41	(0.18, 0.65)	0.062
TREM1	Triggering receptor expressed on myeloid cells 1	0.62	(0.05, 1.18)	0.999
X_5 z-score				
CCL19	C-C motif chemokine 19	-0.53	(-0.82, -0.25)	0.048
PTH1R	Parathyroid hormone 1 receptor,	0.53	(0.04, 1.01)	0.908
BTN3A2	Butyrophilin subfamily 3 member A2	0.64	(0.05, 1.23)	0.908
CXADR	Coxsackievirus and adenovirus receptor	0.60	(0.04, 1.16)	0.908

Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in one second; R_5, respiratory resistance at 5 Hz; X_5, respiratory reactance at 5 Hz.

No systemic protein concentrations were significantly associated with postexercise airway responses (ΔFEV_1, ΔR_5, ΔX_5) after correction for multiple testing. However, five proteins demonstrated significant interactions with atopy, suggesting that allergic sensitization modifies the relationship between systemic inflammatory profiles and airway physiology. Associations of protein levels and postexercise airway responses in analyses stratified by atopy are shown in figure 5.

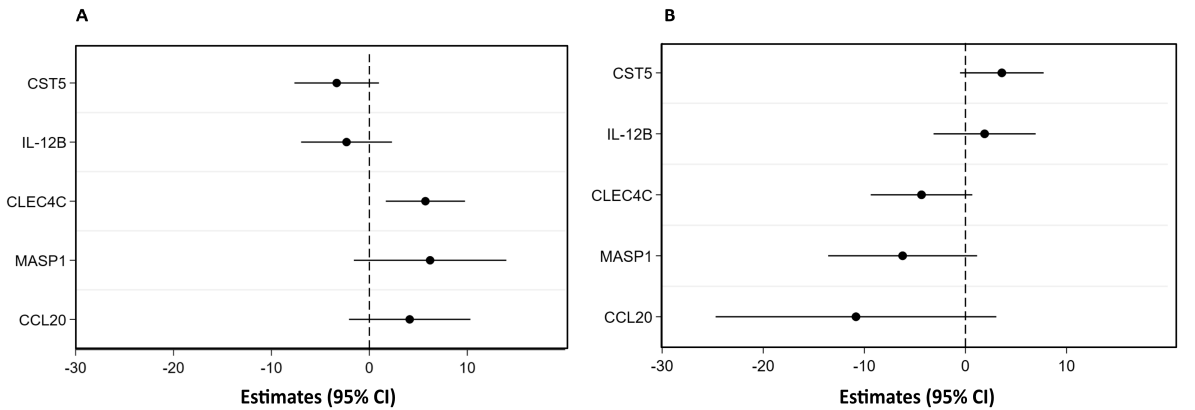

Figure 5. Associations between levels of plasma proteins and airway response after exercise challenge in analyses stratified by atopy, using linear regression models adjusted for sex. The direction of association is shown on the x-axis (negative to the left and positive to the right). Non-atopic in panel A and atopic in panel B. Only proteins with significant interaction term protein x atopy in relation to airway response after exercise challenge were analyzed. In the models with CST5, IL12B, CLEC4C and MASP1 the outcome was ΔFEV_1 while for CCL20 the outcome was ΔR_5.

CST5, Cystatin-D; IL-12B, Interleukin-12 receptor subunit beta-1; CLEC4C, C-type lectin domain family 4 member; MASP1, Mannan-binding lectin serine protease 1; CCL20, C-C motif chemokine 20; CI, confidence interval; FEV_1, forced expiratory volume in one second; R_5, respiratory resistance at 5 Hz.

Discussion

This thesis investigated the prevalence and longitudinal course of EIB and EILO among young athletes, and examined the relationships between respiratory symptoms, exhaled nitric oxide, and postexercise airway responses in both athletes and nonathletes. Furthermore, it examined systemic correlates of lung function and airway responses to exercise in nonathletes. The cross-sectional findings demonstrated that EIB was relatively common, affecting approximately one-quarter of participants, whereas EILO was less prevalent, occurring in about 8% of the athlete cohort. Notably, self-reported exercise-induced dyspnea showed limited diagnostic value in identifying underlying abnormal airway physiology. The longitudinal follow-up revealed that both EIB and EILO represent dynamic, rather than static, conditions during adolescence, with evidence of both new-onset and remitting cases over a two-year period. This underscores the need for repeated objective assessments as athletes mature and training intensity increases. Importantly, incident EIB was associated with the presence of asthma-like symptoms at baseline and the risk increased with the number of reported symptoms, whereas no associations were found with FeNO levels, self-reported aeroallergy, exercise-induced symptoms, or sex. Oscillometry and spirometry offer complementary information in detection of exercise-induced airway obstruction. FeNO was associated with EIB in nonathletes, but not in athletes, suggesting different mechanisms that may underlie airway responses to exercise in these populations. Finally, proteomic analyses identified the chemokine CCL19 to be related to low baseline lung function, while systemic inflammation related protein levels were not significantly associated with postexercise airway responses.

Prevalence and incidence of EIB in adolescent athletes

The estimated prevalence of EIB in paper I was 23.1%, exceeding the rates previously reported among adolescents in the general population.[52] These findings are in line with those of Jonckheere *et al.*, who observed a 24.5% prevalence of EIB among young athletes aged 12–13 years.[42] Furthermore, self-reported exercise-induced dyspnoea was found to be a poor predictor of objectively verified EIB. This observation aligns with prior research conducted in adult athletes,[37, 100] but contrasts with findings from a study involving adolescents in the general population.[74] Consequently, our results suggest that

young athletes early in their sporting careers exhibit EIB characteristics more akin to those of adult athletes than to their non-athletic peers. The observed discrepancy between subjective symptom reports and objective diagnostic outcomes highlights the importance of systematic EIB screening approaches in young athletes.[30, 44] Early detection and appropriate management may mitigate the risk of future airway dysfunction and thus, contributing to the promotion of respiratory health and enhancement of athletic performance.[16]

In paper II, a considerable proportion of participants had incident EIB at follow-up, suggesting that repeated assessments of airway reactivity to hyperpnoea over time may be important in young athletes. Longitudinal investigations of EIB in athletic populations remain limited, but Knöpfli *et al.* have reported that three out of seven developed EIB during a two-year follow-up time in a small study of adult triathletes.[66] Stenrud *et al*. demonstrated that high-level cross-country skiers older than 25 years exhibited a higher prevalence of airway hyperresponsiveness compared with younger skiers[41]. These findings collectively imply that cumulative years of athletic participation may contribute to the development of respiratory pathology in athletes.

Experiencing multiple asthma-like symptoms — primarily occurring outside of exercise — at the time of entering sports high school was associated with incident EIB by the third year of high school. Grassi *et al*. have previously advocated for the use of composite symptom scores to assess asthma severity,[93] and Sunyer *et al*. demonstrated an association between higher composite scores and incident asthma in a large population-based study.[101] Wheeze has previously been associated with EIB in high school athletes,[102] though in most studies of EIB in athletic populations, questions of respiratory symptoms have previously mainly focused on symptoms during or directly after exercise.[37, 100] In contrast, a cross-sectional study of skiers found that asthma-like symptoms had low predictive value for concurrent airway hyperresponsiveness.[10] Although it may seem intuitive to focus on exercise-related symptoms, our findings indicate that respiratory symptoms occurring outside of exercise contexts may provide valuable information when identifying young athletes at risk of developing EIB. The observation that exercise-induced respiratory symptoms poorly predict incident EIB aligns with several cross-sectional studies that have found no consistent relationship between EIB and exercise-related symptoms.[36, 37, 103]

Baseline FeNO demonstrated low predictive value for incident EIB, consistent with previous cross-sectional studies in adult athletes where FeNO did not distinguish between EIB-positive and EIB-negative individuals.[104, 105] However, our results contrast with studies conducted in children and adolescents (nonathlete populations), where elevated FeNO levels have been linked to objective evidence of concurrent EIB,[74, 106] finding we later confirmed in paper III.

No significant association was found regarding self-reported aeroallergy at baseline and incident EIB. This finding diverges from the study by Helenius

et al., which reported significant associations between allergic sensitization and airway hyperresponsiveness in swimmers and long-distance runners.[31] Such discrepancies may partly reflect methodological differences, as aeroallergy in the present study was self-reported rather than objectively confirmed. Variations in training environments may also contribute, as our cohort did not include swimmers, and a substantial proportion of participants were engaged primarily in indoor sports.

Oscillometry to measure EIB

In paper III, the degree of concordance between EIB defined by spirometric change (ΔFEV_1) and oscillometric change (ΔR_5) was modest across both athletes and nonathletes. Approximately half of the participants who met the EIB criterion based on ΔFEV_1 also exhibited a positive response according to ΔR_5, whereas fewer than half of those identified as EIB-positive by ΔR_5 fulfilled the spirometric criterion. This partial overlap suggests that, although both methods assess airway narrowing, they operate under different physiological conditions and may capture airway changes at distinct levels of the respiratory tract. Specifically, spirometry reflects alterations in larger, central airways during forced expiratory maneuvers, while oscillometry evaluates resistance and reactance in the peripheral airways during quiet breathing. As such, the two approaches may detect different phenotypic expressions or subtypes of exercise-induced bronchoconstriction.[107] Oscillometry may therefore complement spirometry also in the context of bronchial provocation by providing insight into airway mechanics not captured by conventional tests, underscoring its potential role in comprehensive airway assessment in both children and adults.[108]

The limited agreement between ΔFEV_1 and ΔR_5 observed here aligns with earlier findings in adult athlete populations[109] and in a prior investigation involving adolescents by our research group.[110] In contrast, studies involving individuals with diagnosed or suspected asthma have reported a much stronger concordance between oscillometric indices and spirometric responses following bronchial provocation.[98, 111, 112] Such discrepancies may be attributable to differences in study populations, the underlying severity and mechanisms of bronchoconstriction, and variations in diagnostic thresholds used across studies.

Investigation of EIB in adolescents – influence of athletic engagement

In paper III, in order to explore potential inflammatory and symptomatic correlates of postexercise airway narrowing, the associations between FeNO, self-

reported respiratory symptoms, and postexercise airway responses (measured by spirometry and oscillomtery) were evaluated in athletes and nonathletes.

Among nonathletes, weak but significant correlations were observed between baseline FeNO and postexercise airway responses (ΔFEV_1, ΔR_5 and ΔX_5), whereas no such correlations were detected in athletes. To the best of our knowledge, this is the first population-based study to concurrently examine FeNO and postexercise responses using both spirometry and oscillometry. Previous findings have demonstrated similar correlations in children with asthma or those at elevated asthma risk, where higher FeNO predicted greater bronchoconstriction following exercise.[72] Additionally, Malmberg *et al*. reported comparable associations between FeNO and oscillometric responses in young wheezy children,[113] aligning with the present observations in nonathletes.

When elevated FeNO (≥ 25 ppb) was analyzed as a potential predictor of EIB, significant associations were observed for EIB (defined by ΔFEV_1 and ΔR_5 respectively) in nonathletes but not in athletes. These findings mirror earlier work in schoolchildren with asthma, where FeNO effectively predicted EIB[71], and from studies in athletes, where FeNO has shown limited predictive value[75]. Conversely, Goossens *et al.* recently suggested that FeNO may still be relevant in atopic athletes, implying that differing inflammatory mechanisms—type 2 versus non–type 2—may underlie EIB in these groups.[43] Our results remained consistent in the athlete group after sensitivity analyses stratified by self-reported aeroallergy. Indeed, previous research indicates that many athletes with EIB exhibit non–type 2 airway inflammation and therefore display low FeNO levels,[30] whereas EIB in the general population is often associated with type 2 inflammatory pathways.[114]

In nonathletes, self-reported wheeze correlated with both spirometric and oscillometric airway responses, whereas exercise-induced dyspnea related only to ΔFEV_1. These associations imply that wheeze may reflect peripheral airway responses more effectively detected through oscillometry. Similar findings were reported by Qvarnström *et al*., who found oscillometric indices to be linked with respiratory symptoms even in individuals with normal spirometry[115]. Among athletes, however, neither wheeze nor exercise-induced dyspnea correlated with objective airway responses, consistent with previous evidence showing poor agreement between symptoms and EIB in both clinical and athletic populations.[109, 116] Thus, objective testing remains essential for confirming EIB, as symptom-based diagnosis alone is unreliable.[20]

Collectively, these findings suggest that FeNO levels and self-reported symptoms may serve as valuable indicators for identifying nonathletic adolescents who should undergo EIB testing, whereas broader availability to objective EIB assessment remains paramount for individuals regularly engaged in athletic activities on a regular basis.

Prevalence and course of EILO in adolescent athletes

The estimated prevalence of EILO in the paper I was 8.1%, a rate slightly higher than that reported in a cross-sectional study of adolescents from the general population[52]. Irewall *et al.* found an even higher prevalence of EILO (27%) in elite cross-country skiers, a group known for high ventilatory demand and frequent airway complaints.[54] In clinical populations of athletes referred to a tertiary respiratory clinic for exercise-related symptoms, EILO has been reported in 35-72% of participants.[55, 117] The greater prevalence reported in the cited studies compared with paper I may indicate a gradual increase in EILO prevalence among athletes as they progress from adolescence into early adulthood, possibly linked to the cumulative effects of a prolonged high training load during continued athletic participation. However, the higher reported EILO prevalence could in part be explained by methodological differences, including study design, inclusion criteria, and population selection—most notably between symptom-based referral cohorts and unselected athletic populations.

EILO was observed at comparable rates among individuals with and without self-reported exercise-induced dyspnea, suggesting that respiratory symptoms alone provide a poor indication of the condition. This illustrates the diagnostic limitations of relying exclusively on symptoms,[60] since some athletes may display laryngeal findings in concordance with EILO without perceiving any breathing difficulties,[54, 118] whereas respiratory symptoms are reported by some athletes in the absence of objective findings of EILO.[54, 55] Taken together, these observations emphasize the need for a combined approach where both perceived symptoms and objective assessments are considered in the evaluation of EILO.

In paper I, a numerically higher proportion of females than males exhibited positive CLE test results; however, no statistically significant sex difference in EILO prevalence was observed. This finding is consistent with a previous population-based study in adolescents,[52] yet contrasts with reports from clinically referred cohorts evaluated for exercise-related respiratory symptoms, in which females constitute the vast majority.[55, 117] The relatively small number of EILO positive cases and modest dropout among male participants may have limited the statistical power to detect sex-related differences in paper I.

The supraglottic subtype was the most common form of EILO, observed in four of the eight participants, while two exhibited the purely glottic type and another two showed a combination of glottic and supraglottic involvement. In line with this finding, several previous studies have found that supraglottic EILO is the most prevalent subtype of the condition.[54, 119] One possible explanation is that supraglottic closure typically occurs earlier during exercise than glottic closure.[120] As a result, individuals may discontinue exercise during CLE test before glottic obstruction develops, potentially leading to an under classification of cases exhibiting both supraglottic and glottic involvement.

In paper II five out of 27 participant who performed a CLE test at follow-up were classified as having EILO, whereof three were classified as incident EILO. All of the EILO cases at follow-up were classified as supraglottic. To date, no large-scale epidemiological data exist on the natural history of EILO, but our observations support earlier work by Maat *et al.,*[68] which indicated that supraglottic EILO often persists over time. These findings align with a study of elite skiers, where supraglottic obstruction was the predominant and most stable form of EILO over time, showing limited remission despite conservative management with advice on breathing techniques.[69] Surgical treatment (supraglottoplasty or epiglottoplasty) of severe supraglottic EILO has been reported beneficial in selected cases.[65, 121-123] However, there is a lack of prospective randomized controlled trials evaluating surgical and other treatment approaches for EILO. Taken together, our findings—along with previous research on EILO in athletes—suggest a potential link between athletic training load and the persistence of this condition. Overall, these results highlight that supraglottic EILO remains the predominant and persistent subtype among young athletes, underscoring the importance of long-term monitoring and the development of targeted treatment strategies.

Systemic inflammation and immune markers and lung function in nonathletes

In paper IV, we explored associations between systemic inflammatory and immune-regulatory biomarkers and lung function, both at rest and following an exercise challenge, assessed via spirometry and oscillometry. Among the 135 plasma proteins analysed, C-C motif chemokine 19 (CCL19) showed a significant inverse association with baseline lung function after adjustment for multiple testing. Specifically, higher CCL19 concentrations were linked to lower FEV_1% predicted and reduced X_5 z-scores, the latter suggesting impaired small airway mechanics. CCL19, a homeostatic chemokine, facilitates dendritic cell and T lymphocyte migration to lymphoid tissues and contributes to immune regulation.[124] Associations, similar to our findings, have been reported by Wang *et al*., who found higher circulating CCL19 linked to lower lung function in young adults.[125] Elevated CCL19 levels have also been implicated in allergic airway inflammation in animal models[126, 127] and in human airway tissue.[128] Recent evidence indicates that CCL19 can promote Th2 differentiation, intensifying type 2 immune responses and allergic airway inflammation[129], which could contribute to the observed reductions in lung function.

Additionally, tumour necrosis factor (TNF) showed a trend toward positive association with R_5 z-scores, supporting its established role as a key mediator of airway inflammation and remodeling.[130, 131] TNF enhances airway smooth muscle tone, mucus secretion, and epithelial permeability.[131] mechanisms that

can lead to increased airway resistance. Elevated TNF has previously been associated with severe, treatment-resistant asthma.[132] Thus, the observed trend between TNF and R_5 may reflect subclinical inflammatory activity influencing airway resistance, warranting confirmation in larger studies.

Systemic inflammation and immune markers and EIB in nonathletes

In paper IV, no individual plasma protein biomarker showed a significant association with airway responses (measured by ΔFEV_1, ΔR_5 and ΔX_5) following exercise once stringent false discovery rate correction was applied. Since plasma proteins were measured before the exercise challenge, these results likely reflect the dynamic nature of the EIB process, characterized by a rapid and transient release of mast cell mediators immediately following physical exertion. Previous studies demonstrating links between mast cell activation and EIB have typically measured such mediators in urine[133] or induced sputum,[134] capturing acute postexercise inflammatory events rather than baseline systemic profiles. This highlights that exercise-induced inflammatory changes may be short-lived and therefore difficult to detect using single prechallenge proteomic measurements.

Nonetheless, other studies have reported elevated levels of mast cell–associated mediators in exhaled breath condensate among children with EIB,[135] and baseline FeNO has also been linked to the occurrence of EIB in this same adolescent population.[74] Furthermore, airway hyperresponsiveness to direct bronchial provocation in children has been associated with markers of eosinophil activation, such as eosinophil-derived neurotoxin and eosinophil cationic protein.[136] Together, these findings suggest that although single baseline proteomic measurements may not adequately capture transient exercise-induced responses, resting inflammatory profiles—particularly those reflecting mast cell and eosinophil activity—may still provide valuable insights into individual susceptibility to EIB.

Interestingly, interaction analyses revealed that associations between several plasma proteins and airway responses—measured as changes in FEV_1 or R_5 following exercise—differed according to atopic status. Specifically, significant interactions were observed for CLEC4C, MASP1, CST5, IL12B, and CCL20, indicating that the influence of systemic inflammatory mediators on airway responsiveness may vary between atopic and non-atopic adolescents. These proteins are known to participate in both innate and adaptive immune processes, including antigen presentation, complement activation, cytokine signalling, and mucosal defence. The divergent associations observed between atopic groups may therefore reflect distinct inflammatory endotypes influencing airway reactivity during exercise.

This interpretation aligns with previous evidence showing that airway inflammation and airway hyperresponsiveness are closely linked to allergic sensitization. Atopic individuals tend to display a predominance of eosinophilic inflammation and IgE-mediated immune pathways, which contribute to increased airway sensitivity.[113, 137] Moreover, elevated FeNO levels have been shown to be more prevalent in atopic individuals and are associated with increased airway hyperresponsiveness.[138] Taken together, these findings support the notion that the interplay between systemic immune activation and atopy may shape the degree of airway responsiveness, emphasizing the importance of considering atopic status when interpreting inflammation and immune related biomarker associations in studies of airway physiology.

Methodological considerations

The interpretation and implications of study findings are dependent on the study's inherent strengths and limitations. Reliability concerns the consistency or stability of measurements across repetitions of the method and can be evaluated through test–retest reliability, inter-rater reliability, or intra-rater reliability analyses. Validity refers to the extent to which a method accurately measures what it is intended to measure. Key dimensions of validity include sensitivity (true positive rate)—the proportion of individuals with a condition correctly identified—and specificity (true negative rate)—the proportion of healthy individuals accurately classified as healthy. In questionnaire-based research, validity may be compromised by recall bias, whereby participants systematically misremember or misreport information.

External validity concerns the generalizability of the findings beyond the study sample, which can be affected by participation bias arising when certain individuals are more or less likely to participate in research, resulting in a non-representative sample of the population of interest.

The overall methodological framework across the included studies was characterized by the application of standardized procedures for assessing EIB and EILO i.e., standardized EIB testing and CLE testing. These objective diagnostic methods enhanced internal validity by reducing reliance on self-reported symptoms. Nonetheless, several methodological aspects warrant critical reflection.

The cross-sectional design of paper I, III and IV limited causal inference, whereas the longitudinal design of paper II provided valuable insight into the course of EIB and EILO, but was subject to participant attrition, particularly regarding CLE testing, which may have introduced selection bias and affected the representativeness of the findings.

Recruitment of athletes from sports high schools ensured a homogenous cohort of trained adolescents, facilitating control of training exposure but potentially limiting generalizability to less physically active peers.

The questionnaire response rate in paper I was fairly good (66.8%); however, selection bias cannot be excluded, as no information was available for athletes who chose not to participate in the study.

Questionnaire

The questionnaire employed across all the included papers is based on questionnaires developed and validated for asthma,[139, 140] hence the questionnaire employed has not been scientifically tested for reliability and validity in studies of EIB nor EILO. However, the questionnaire has previously been employed in studies of EIB and EILO.[52, 54] To minimize recall bias in the included studies, participants were instructed to report respiratory symptoms limited to the 12 months preceding study participation. For nonathlete participants, the questionnaires were also completed jointly by the adolescents and their guardians.

Recently, other questionnaires have been proposed as part of a diagnostic algorithm for EIB in young athletes.[43] Furthermore, progress has been made in development of a questionnaire for patient reported outcomes in EILO.[141] These tools have the potential to provide significant value in both clinical settings and future research, but require validation in larger cohorts prior to full implementation.

EIB test

In the included papers, the EIB test combined dry air inhalation with high-intensity exercise, providing a rigorous indirect bronchial challenge with higher sensitivity than a challenge with exercise alone, but potentially with reduced specificity. This stringent protocol optimized detection of exercise-induced airway narrowing by ensuring a strong physiological stimulus and minimizing false negatives. However, such rigor may also have identified individuals as EIB-positive who would not exhibit measurable bronchoconstriction under their usual training conditions, depending on sport type, environment, and exercise intensity. Although field- or sport-specific tests[142-144] may better reflect habitual exercise conditions and environmental triggers, the standardized laboratory-based dry air exercise test offers superior comparability in longitudinal studies through control of confounding variables, such a variability in ambient conditions, allergen exposure and exercise intensity.[145]

The EIB test protocol employed a target heart rate exceeding 90% of the predicted maximum, which is slightly above the generally recommended threshold of >85% of maximum, commonly used as a surrogate for achieving 60% of maximal voluntary ventilation.[39] The higher target followed recommendations for highly trained athletes to ensure sufficient ventilatory load,[145] consistent with evidence from pediatric studies underscoring the need for adequate exercise intensity to reliably detect EIB.[146]

Across all papers, only a single EIB test was performed, which may have compromised internal validity, as the bronchoconstrictive response can fluctuate over time. Repeated testing has been recommended, particularly in cases of mild or borderline EIB among athletes, to allow for more robust confirmation or exclusion of the condition.[147] On the other hand, a laboratory-based dry air exercise test, such as the one used in the present thesis, has been shown to demonstrate good reproducibility.[148]

The EIB protocol, which included both oscillometry and spirometry measurements at each post-exercise time point, was challenging to conduct due to time constraints. Oscillometry was performed before spirometry at each interval to minimize the impact of deep inspiratory maneuvers from the spirometry on bronchial tone.[47] However, the short time intervals between postexercise measurements may still have allowed this effect to occur, potentially resulting in bronchodilation being present during the subsequent oscillometry measurement.

EIB was defined as a ≥10% decrease in FEV_1 at any time point following the challenge compared with baseline values, in accordance with recommendations.[39] In athletes, applying the ≥10% threshold yields high sensitivity but may result in a relatively large proportion of asymptomatic individuals being classified as having EIB.[149] Increasing the threshold to a ≥15% decrease in FEV_1 would enhance the specificity of the diagnosis.[150] As the nondyspnea group in paper I had a higher proportion of EIB positive participants, sensitivity analyses using the ≥15% threshold were conducted. The results indicated fewer EIB positive participants overall, while the distribution between the groups remained similar.

To enhance internal validity and minimize experimenter expectancy effects, investigators performing the EIB tests were blinded to whether participants had reported exercise-induced dyspnea in the questionnaire.

CLE test

In paper I and II, the CLE test was employed to assess EILO. The CLE test is the diagnostic method for EILO, as it enables direct visualization of the larynx during peak exercise.[51] The continuous visualization of the larynx during exercise is crucial since EILO is effort-dependent and promptly normalizes after exercise.[151] The CLE test was performed on a cycle ergometer instead of on a treadmill, as in the original test description of the method.[51] The use of a cycle ergometer may have provided a lower exercise stimulus than treadmill running, potentially leading to some false-negative EILO results. Nevertheless, participants were required to exercise until exhaustion, typically exceeding 90% of their estimated maximum heart rate. Moreover, previous studies have shown that CLE testing using other exercise modalities is feasible and yields comparable EILO detection to treadmill-based protocols.[152-154]

Laryngeal obstruction was graded using the visual score proposed by Maat *et al.*[99], which is the most widely used method in both research and clinical

practice. However, this method has certain limitations related to reliability, as test–retest variability and inconsistent inter- and intra-rater agreement have been reported.[99, 155] Thus, while the visual grade score remains practical, it may introduce measurement variability, underscoring the need for validated objective assessment tools for EILO. To date, no objective grading system for laryngeal obstruction is available. However, alternative methods have been proposed, including software-based assessments[156] and automated evaluation using machine learning approaches.[157]

Lastly, to enhance internal validity and minimize experimenter expectancy effects, investigators performing the CLE tests were blinded to whether participants had reported exercise-induced dyspnea and to the results of the prior EIB test.

Elevated FeNO

In Paper III, an elevated FeNO level was defined as ≥25 ppb, consistent with the American Thoracic Society threshold for low FeNO.[158] This threshold corresponds to the lower limit of "intermediate" FeNO and is widely used as an indicator of type 2 inflammation in both clinical and research contexts.[158] However, fixed FeNO cut-offs do not account for individual characteristics such as sex, height, age, and atopic status, all of which influence normal FeNO ranges.[159, 160] Although personalized reference values have been proposed to address these factors,[160] their diagnostic utility in the context of EIB remains uncertain. Certainly, the use of a standardized threshold enables comparability across studies. Increasing the threshold for elevated FeNO to ≥40 ppb could have improves the specificity for detecting EIB particularly among the athletes, but previous research indicates that this comes at the cost of reduced sensitivity for identifying EIB in athletic population.[75]

Conclusion

This thesis provides a comprehensive examination of airway responses to exercise in adolescents through the integration of epidemiological, physiological, and immunological perspectives. The findings indicate that exercise-induced bronchoconstriction (EIB) is relatively common among adolescent athletes, while exercise-induced laryngeal obstruction (EILO) is less prevalent. However, EILO remains an important condition for clinicians to recognize and consider when caring for young physically active individuals. Notably, self-reported exercise-induced dyspnoea and respiratory symptoms exhibited limited diagnostic accuracy, underscoring the importance of objective assessment methods such as standardized exercise challenge testing and continuous laryngoscopy exercise testing for accurate identification of airway dysfunction.

The longitudinal analyses revealed that both EIB and EILO represent dynamic rather than static conditions during adolescence, with evidence of both incident and remitting cases over time. These observations suggest abnormal airway response to exercise may evolve with increasing training load and physiological maturation, highlighting the need for periodic re-evaluation of young athletes presenting with respiratory complaints. Furthermore, spirometry and oscillometry are two techniques that capture distinct but complementary aspects of airway mechanics. Fractional exhaled nitric oxide was associated with EIB among nonathletes but not among athletes, implying divergent underlying mechanisms and inflammatory pathways depending on physical activity exposure and airway conditioning.

Proteomic analyses identified the chemokine CCL19 as a systemic biomarker associated with lower baseline lung function, implicating immune and inflammatory processes in the regulation of pulmonary function even in otherwise healthy adolescents. Although systemic inflammatory markers were not directly associated with postexercise airway responses, the observed interactions with atopy suggest that allergic sensitization modifies systemic inflammation–airway relationships. These findings point to a complex interplay between physiological, environmental, and immunological factors that shape airway function and reactivity during a critical stage of growth and development.

In summary, this thesis contributes to the understanding of airway disorders in relation to exercise in adolescence by elucidating their prevalence, course, physiological heterogeneity, and immunological correlates. The findings emphasize the necessity of incorporating objective diagnostic approaches,

longitudinal monitoring, and individualized evaluation into clinical and sports medicine practice. By refining diagnostic accuracy and identifying potential biomarkers, this work may contribute to improved strategies for the prevention, diagnosis, and management of exercise-induced airway dysfunction, thereby supporting respiratory health and sustained participation in physical activity among adolescents.

Future perspectives

From a broader perspective, these results carry important implications for both clinical practice and public health. The high prevalence of undetected or misdiagnosed airway dysfunction among youth engaged in organized sports underscores the need for structured screening protocols and increased awareness among coaches, healthcare providers, and educators. From a clinical standpoint, these findings highlight the importance of incorporating objective diagnostic testing—such as standardized exercise challenge and laryngoscopic evaluation—into the assessment of adolescents presenting with respiratory symptoms in the context of physical activity ad exercise. Clinicians should be aware that conventional asthma diagnostics and symptom-based evaluation may fail to identify conditions such as exercise-induced bronchoconstriction or laryngeal obstruction, leading to inappropriate or insufficient treatment. Early and accurate identification, followed by individualized management including pharmacological and non-pharmacological interventions, can prevent unnecessary medication use, optimize respiratory health, and enable continued engagement in sports.

Furthermore, coordinated collaboration between sports medicine practitioners, general healthcare providers, and school health services is essential to ensure continuity of care and follow-up, particularly in high-performance training environments such as in Swedish sports high schools. Future research should aim to delineate the mechanisms linking airway inflammation, environmental exposures, and training intensity, as well as to develop validated screening tools and clinical algorithms applicable in both athletic and general adolescent populations. Additionally, the role of oscillometry as a stand-alone method for assessing airway responses during bronchial challenges remains uncertain. The interpretation of abnormal oscillometric airway response patterns is not yet fully understood, particularly in cases of mild to bronchoconstriction. Future research should aim to determine optimal threshold values for defining a positive airway response in larger, well-characterized populations.

Collectively, the insights from this thesis contribute to a foundation for evidence-based clinical and public health recommendations that could promote airway health through early detection, and safe, inclusive participation in sports at each adolescent's desired level.

Sammanfattning på Svenska – Summary in Swedish

Denna avhandling undersöker luftvägsreaktioner vid fysisk ansträngning hos ungdomar med fokus på förekomst, utveckling och bakomliggande mekanismer till ansträngningsutlöst bronkkonstriktion (exercise-induced bronchoconstriction, EIB) och ansträngningsutlöst laryngeal obstruktion (exercise-induced laryngeal obstruction, EILO). Genom epidemiologiska, fysiologiska och immunologiska analyser studerades både ungdomar vid idrottsgymnasium och ungdomar från den allmänna befolkningen.

Syftet var att öka kunskapen om ansträngningsutlösta luftvägstillstånd under tonåren och bidra till förbättrad diagnostik och uppföljning. Fyra delstudier genomfördes: studie I–II undersökte förekomst och utveckling under en tvåårsperiod av EIB och EILO hos idrottande ungdomar; studie III analyserade samband mellan självrapporterade symtom, utandad kvävemonoxid (FeNO) och lungfunktionsförändringar efter asnträngning; studie IV kartlade kopplingar mellan inflammatonsrelaterade proteiner i plasma, atopi, lungfunktion och EIB.

Resultaten visade att EIB var vanligt (23 %) medan EILO förekom hos cirka 8 %. Självrapporterade symtom hade låg diagnostisk tillförlitlighet, vilket understryker behovet av objektiva tester. Både EIB och EILO visade sig vara dynamiska tillstånd med nya fall såväl som fall som gick i regress över tid. Hos icke-idrottare, men inte hos idrottare, var självrapporterade symptom samt förhöjda FeNO-nivåer kopplade till EIB, vilket antyder olika bakomliggande mekanismer. Analyserna av inflammationsrelaterade proteiner i plasma identifierade CCL19 som en markör associerad med lägre lungfunktion, vilket tyder på att immunologiska processer påverkar luftvägarna även hos övrigt friska ungdomar.

Avhandlingen visar att ansträngningsutlösta luftvägsbesvär är vanliga bland ungdomar som idrottar, besvären är inte sällan oupptäckta och kräver objektiv diagnostik och uppföljning. Ur ett kliniskt och folkhälsoinriktat perspektiv betonas behovet av strukturerad screening av idrottare, ökad kunskap bland tränare och vårdpersonal samt tvärprofessionell samverkan. Tidig identifiering och individuell behandling kan förbättra luftvägshälsa, välbefinnande och prestationsförmåga samt bidra till säkert och hälsosamt deltagande i fysisk träning och idrott för ungdomar.

Acknowledgements

During my research education, I have been fortunate to have many wonderful people around me in all the different circles of my life. I would like to express my love and gratitude to everyone who has brought light and laughter to me over the past seven years.

To my supervisors **Andrei and Henrik**, you have truly been my dream team. **Andrei**, thank you for your enormous patience and for generously sharing your deep skills in the world of epidemiology, pulmonology and exercise physiology. Your positive attitude and support have indeed lifted me up from many dark places. **Henrik**, thank you for your contagious enthusiasm and passion for physiotherapy and research. Without you I would surely still think of research as something terrifying and unreachable. Your steady and generous mentorship—both in the clinic (even before my PhD) and in science—has meant more than I can say. I look forward to continuing to learn from you in the future.

To my colleagues and co-authors at the ENT-department, **Elisabet, Katarina** and **Leif.** Thank you for fantastic collaboration in the CELADY-project. A special thanks to **Nilla** for invaluable support during the data collection in CELADY.

To my co-authors **Kjell, Margareta** and **Christer**. Thank you for so freely sharing your extensive knowledge in science and scientific writing.

To all the participants in the **projects ANDAS and CELADY**. Thank you for participating in research – you have contributed to an important piece in the puzzle of breathing problems and exercise.

My sincere gratitude to **VO Geriatrik, Rehabiliteringsmedicin och Smärtcentrum** and the **Physiotherapy organization at Akademiska sjukhuset** for giving me the opportunity to alternate between research and clinic. I realize that scheduling has been a challenge during my research education and I am very grateful for the efforts made by the organization.

To everyone at the **Department for Respiratory, Allergy and Sleep Research and Clinical Physiology Research.** Thank you for everything from "fika chatting" to logistics and technical support in the lab. A special thank you to the one and only **Gunnis** for all the support through the years, both administrative and emotional. A big thanks also to **Gunilla** for providing smiles and coffee in the very early mornings in the lab during the CELADY data collection. To **Jenny,** thank you for sharing your experiences of the research world and for always being available for discussions on clinical as well as scientific issues.

To my friends at **EpiHubben** at **Uppsala University**. Thank you for letting me be a part of your creative and positive epi-environment. I have learned so much about epidemiology, statistics, strategies for Vasaloppet and even knitting patterns. I have really appreciated **Jonas'**, and in the last year also **Luka's**, calls for coffee in the morning. A special thank you to **Olga** for so generously sharing your deep knowledge in epidemiology and omics research and for our lovely talks on the world of research, exercise routines, family and life.

To everyone in the research group **Physiotherapy and Behavioral Medicine** at Uppsala University. Thank you for inspirational and joyful discussions on physiotherapy and research. To **Pernilla,** thank you for generously sharing your profound insights in physiotherapy research. A special thank you to **Sofia** for leading the way through the final part of our parallel PhD journeys. I felt safe knowing you were a month ahead of me.

To everyone at the **Department for Respiratory Medicine** at **Akademiska sjukhuset**, thank you for great team work and so much laughter. Special thanks to **Sofie** for steady leadership of the Home mechanical ventilation unit. To **Andreas** and **Mirjam**, thank you for contributing to an environment where science and clinic are truly united in the everyday work.

To everyone at the **Physiotherapy department** and **Uppsala CF center at Akademiska barnsjukhuset**. Thank you for friendship and support through the years. A very special thanks to **Ewa** for being a wonderful friend and colleague. You have been with me ever since I first came to the CF center as a physio student, always encouraging and supporting me along the way. Thank you for everything!

To my fabulous physiotherapy colleagues **Reka, Sara** and **Micke,** thank you for your friendship making work days both continuously interesting and enjoyable. Reka, thank you for asking me a million questions that I don't know the answers to, we learn together. I am also very grateful to you for introducing me to qualitative research. Sara, lucky us that you found your way home to

respiratory physiotherapy. Thank you for your curious and contemplative approach counterweighting the more hot-headed colleagues (perhaps me especially). Micke, an immense thank you for being my co-pilot and pillar in clinic. I've really cherished our conversations about clinical challenges, science, and life in general.

To my friend **Maria**. Thank you for support and friendship through the years. You took me in as a rookie in respiratory physiotherapy some twenty years ago and guided my way with humor and kindness. I truly miss working with you but I'm so thankful for the lasting friendship we share.

To all of my friends in **Svenska ju-jutsuförbundet**. Thank you for the warm and supporting environment you create, filled with equal parts hugs and bruises.

To everyone in **Uppsala ju-jutsuklubb**. Thank you for invaluable encouragement and support in the past 33 years. It is an honor and a privilege to be part of an organization striving for technical excellence and strong national leadership and at the same time creating an inclusive and safe learning environment. A special thanks to **Tony** for your confidence in me and for challenging me to continuously move forward. To my dear friend **Ylva,** thank you for making countless hours of training in the dojo fun and filled with laughter.

To our extra family member **Ludde**. Many times, you drive me crazy but even more often you make me laugh out loud. Thank you for challenging my way of thinking and for giving me new goals for my future exercise routines.

To the **Ersson** family. **Gudrun and Urban**, thank you for your love and support through the years. Your support and care have been paramount in helping me juggle clinical work, data collection, Friskis & Svettis classes, and ju-jutsu activities all across the country. Thank you! **Per, Marica, Johan & Karin** thank you for encouragement and all the fabulous wine & dine moments.

To the **Sahlin** family. To my mother, **Anna-Lena**, thank you for your unwavering care and support for me and my family. You have always been my steadfast supporter, even in moments when I felt I had taken on too much. To my father, **Jörgen,** and my **Lena**, thank you for encouragement and essential support in every part of my life. Thank you for giving me confidence and a solid foundation. To my brother **Erik** and my sister **Malin**. I'm so grateful you're part of my life, even if time and distance sometimes keep us apart.

To my children, **Vidar** and **Tyra**. You are my greatest pride in life. Thank you for filling it with love and laughter.

To **Mats,** wrestling you down in the dojo was the best decision I ever made. Without you, life would leave me both unhappy and hungry. Thank you for your patience with all my adventures and for giving me so much love!

This thesis was funded by the Swedish Research Council, the Swedish Heart and Lung Foundation, the Swedish Asthma and Allergy Association, the Knut and Alice Wallenberg Foundation, the Hesselman Foundation, the Signhild Engqvist Foundation, the Bror Hjerpstedt Foundation, the Gillbergska Foundation and the Uppsala County Association against Heart and Lung Diseases and by ALF (Agreement for Medical Education and Research).

References

1. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. British Journal of Sports Medicine. 2020;54(24):1451.
2. Johansson H, Norlander K, Malinovschi A. Increased prevalence of exercise-induced airway symptoms – A five-year follow-up from adolescence to young adulthood. Respiratory Medicine. 2019;154:76-81.
3. Johansson H, Norlander K, Hedenstrom H, Janson C, Nordang L, Nordvall L, et al. Exercise-induced dyspnea is a problem among the general adolescent population. Respir Med. 2014;108(6):852-8.
4. Yeatts K, Johnston Davis K, Peden D, Shy C. Health consequences associated with frequent wheezing in adolescents without asthma diagnosis. Eur Respir J. 2003;22(5):781-6.
5. Turcotte H, Langdeau J-B, Thibault G, Boulet L-P. Prevalence of respiratory symptoms in an athlete population. Respiratory Medicine. 2003;97(8):955-63.
6. Hallstrand TS, Curtis JR, Koepsell TD, Martin DP, Schoene RB, Sullivan SD, et al. Effectiveness of screening examinations to detect unrecognized exercise-induced bronchoconstriction. J Pediatr. 2002;141(3):343-8.
7. Langdeau JB, Day A, Turcotte H, Boulet LP. Gender differences in the prevalence of airway hyperresponsiveness and asthma in athletes. Respir Med. 2009;103(3):401-6.
8. Ringsberg KC, BjÄRneman P, LÖWhagen O, OdÉN A, TorÉN K. Differences in trigger factors and symptoms between patients with asthma-like symptoms and patients with asthma: development of a basis for a questionnaire. Respiratory Medicine. 2002;96(5):305-11.
9. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health. 2012;12:204.
10. Stenfors N. Self-reported symptoms and bronchial hyperresponsiveness in elite cross-country skiers. Respir Med. 2010;104(11):1760-3.
11. Dempsey JA, La Gerche A, Hull JH. Is the healthy respiratory system built just right, overbuilt, or underbuilt to meet the demands imposed by exercise? J Appl Physiol (1985). 2020;129(6):1235-56.
12. Hull JH, Ansley L, Robson-Ansley P, Parsons JP. Managing respiratory problems in athletes. Clinical medicine (London, England). 2012;12(4):351-6.
13. Parsons JP, Craig TJ, Stoloff SW, Hayden ML, Ostrom NK, Eid NS, et al. Impact of exercise-related respiratory symptoms in adults with asthma: Exercise-Induced Bronchospasm Landmark National Survey. Allergy Asthma Proc. 2011;32(6):431-7.
14. Hallstrand TS, Curtis JR, Aitken ML, Sullivan SD. Quality of life in adolescents with mild asthma. Pediatric Pulmonology. 2003;36(6):536-43.

15. Kojima N, Ohya Y, Futamura M, Akashi M, Odajima H, Adachi Y, et al. Exercise-Induced Asthma is Associated with Impaired Quality of Life Among Children with Asthma in Japan. Allergology International. 2009;58(2):187-92.
16. Jackson AR, Hull JH, Hopker JG, Dickinson JW. Impact of detecting and treating exercise-induced bronchoconstriction in elite footballers. ERJ Open Res. 2018;4(2).
17. Dickinson J, McConnell A, Whyte G. Diagnosis of exercise-induced bronchoconstriction: eucapnic voluntary hyperpnoea challenges identify previously undiagnosed elite athletes with exercise-induced bronchoconstriction. Br J Sports Med. 2011;45(14):1126-31.
18. Ansley L, Kippelen P, Dickinson J, Hull JH. Misdiagnosis of exercise-induced bronchoconstriction in professional soccer players. Allergy. 2012;67(3):390-5.
19. Weiler JM, Bonini S, Coifman R, Craig T, Delgado L, Capão-Filipe M, et al. American Academy of Allergy, Asthma & Immunology Work Group report: exercise-induced asthma. J Allergy Clin Immunol. 2007;119(6):1349-58.
20. Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, Hull JH, et al. An Official American Thoracic Society Clinical Practice Guideline: Exercise-induced Bronchoconstriction. American Journal of Respiratory and Critical Care Medicine. 2013;187(9):1016-27.
21. Bonini M, Silvers W. Exercise-Induced Bronchoconstriction: Background, Prevalence, and Sport Considerations. Immunol Allergy Clin North Am. 2018;38(2):205-14.
22. Boulet LP, O'Byrne PM. Asthma and exercise-induced bronchoconstriction in athletes. N Engl J Med. 2015;372(7):641-8.
23. Price OJ, Sewry N, Schwellnus M, Backer V, Reier-Nilsen T, Bougault V, et al. Prevalence of lower airway dysfunction in athletes: a systematic review and meta-analysis by a subgroup of the IOC consensus group on 'acute respiratory illness in the athlete'. British Journal of Sports Medicine. 2022;56(4):213.
24. Aggarwal B, Mulgirigama A, Berend N. Exercise-induced bronchoconstriction: prevalence, pathophysiology, patient impact, diagnosis and management. NPJ primary care respiratory medicine. 2018;28(1):31-.
25. Weiler JM, Anderson SD, Randolph C, Bonini S, Craig TJ, Pearlman DS, et al. Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: a practice parameter. Ann Allergy Asthma Immunol. 2010;105(6 Suppl):S1-47.
26. Rodriguez Bauza DE, Silveyra P. Sex Differences in Exercise-Induced Bronchoconstriction in Athletes: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2020;17(19).
27. Price OJ, Ansley L, Menzies-Gow A, Cullinan P, Hull JH. Airway dysfunction in elite athletes--an occupational lung disease? Allergy. 2013;68(11):1343-52.
28. Del Giacco SR, Firinu D, Bjermer L, Carlsen KH. Exercise and asthma: an overview. Eur Clin Respir J. 2015;2:27984.
29. Rundell KW, Sue-Chu M. Air quality and exercise-induced bronchoconstriction in elite athletes. Immunol Allergy Clin North Am. 2013;33(3):409-21, ix.
30. Couto M, Kurowski M, Moreira A, Bullens DMA, Carlsen K-H, Delgado L, et al. Mechanisms of exercise-induced bronchoconstriction in athletes: Current perspectives and future challenges. Allergy. 2018;73(1):8-16.
31. Helenius IJ, Tikkanen HO, Haahtela T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. British journal of sports medicine. 1998;32(2):125-9.

32. Sallaoui R, Chamari K, Mossa A, Tabka Z, Chtara M, Feki Y, et al. Exercise-induced bronchoconstriction and atopy in Tunisian athletes. BMC pulmonary medicine. 2009;9:8-.
33. Couto M, Stang J, Horta L, Stensrud T, Severo M, Mowinckel P, et al. Two distinct phenotypes of asthma in elite athletes identified by latent class analysis. Journal of Asthma. 2015;52(9):897-904.
34. Haahtela T, Malmberg P, Moreira A. Mechanisms of asthma in Olympic athletes – practical implications. Allergy. 2008;63(6):685-94.
35. Rundell KW, Im J, Mayers LB, Wilber RL, Szmedra L, Schmitz HR. Self-reported symptoms and exercise-induced asthma in the elite athlete. Medicine & Science in Sports & Exercise. 2001;33(2).
36. Weiss P, Rundell KW. Imitators of exercise-induced bronchoconstriction. Allergy Asthma Clin Immunol. 2009;5(1):7.
37. Price OJ, Hull JH, Ansley L, Thomas M, Eyles C. Exercise-induced bronchoconstriction in athletes - A qualitative assessment of symptom perception. Respir Med. 2016;120:36-43.
38. Weiler JM, Brannan JD, Randolph CC, Hallstrand TS, Parsons J, Silvers W, et al. Exercise-induced bronchoconstriction update—2016. Journal of Allergy and Clinical Immunology. 2016;138(5):1292-5.e36.
39. Hallstrand TS, Leuppi JD, Joos G, Hall GL, Carlsen KH, Kaminsky DA, et al. ERS technical standard on bronchial challenge testing: pathophysiology and methodology of indirect airway challenge testing. Eur Respir J. 2018;52(5).
40. O'Byrne PM, Gauvreau GM, Brannan JD. Provoked models of asthma: what have we learnt? Clinical & Experimental Allergy. 2009;39(2):181-92.
41. Stensrud T, Berntsen S, Carlsen KH. Exercise capacity and exercise-induced bronchoconstriction (EIB) in a cold environment. Respir Med. 2007;101(7):1529-36.
42. Jonckheere A-C, Seys S, Dilissen E, Schelpe A-S, Van der Eycken S, Corthout S, et al. Early-onset airway damage in early-career elite athletes: A risk factor for exercise-induced bronchoconstriction. Journal of Allergy and Clinical Immunology. 2019.
43. Goossens J, Vandekerckhove J, Jonckheere AC, Dilissen E, Marain N, Ieven T, et al. Exercise-induced bronchoconstriction in adolescent recreational athletes: Potential screening strategies. Pediatr Allergy Immunol. 2024;35(8):e14220.
44. Goossens J, Decaesteker T, Jonckheere AC, Seys S, Verelst S, Dupont L, et al. How to detect young athletes at risk of exercise-induced bronchoconstriction? Paediatr Respir Rev. 2021.
45. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. American Journal of Respiratory and Critical Care Medicine. 2019;200(8):e70-e88.
46. Tirelli C, Mira S, Italia M, Maggioni S, Intravaia C, Zava M, et al. Applications of Forced Oscillatory Technique in Obstructive and Restrictive Pulmonary Diseases: A Concise State of the Art. Journal of Clinical Medicine. 2025;14(16):5718.
47. SCICHILONE N, KAPSALI T, PERMUTT S, TOGIAS A. Deep Inspiration-induced Bronchoprotection Is Stronger than Bronchodilation. American Journal of Respiratory and Critical Care Medicine. 2000;162(3):910-6.

48. Kaminsky DA, Simpson SJ, Berger KI, Calverley P, de Melo PL, Dandurand R, et al. Clinical significance and applications of oscillometry. Eur Respir Rev. 2022;31(163).
49. King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellacà RL, et al. Technical standards for respiratory oscillometry. Eur Respir J. 2020;55(2).
50. Schmekel B, Smith H. The diagnostic capacity of forced oscillation and forced expiration techniques in identifying asthma by isocapnic hyperpnoea of cold air. European Respiratory Journal.10(10):2243-9.
51. Halvorsen T, Walsted ES, Bucca C, Bush A, Cantarella G, Friedrich G, et al. Inducible laryngeal obstruction: an official joint European Respiratory Society and European Laryngological Society statement. Eur Respir J. 2017;50(3):1602221.
52. Johansson H, Norlander K, Berglund L, Janson C, Malinovschi A, Nordvall L, et al. Prevalence of exercise-induced bronchoconstriction and exercise-induced laryngeal obstruction in a general adolescent population. Thorax. 2015;70(1):57-63.
53. Christensen PM, Thomsen SF, Rasmussen N, Backer V. Exercise-induced laryngeal obstructions: prevalence and symptoms in the general public. Eur Arch Otorhinolaryngol. 2011;268(9):1313-9.
54. Irewall T, Bäcklund C, Nordang L, Ryding M, Stenfors N. High Prevalence of Exercise-induced Laryngeal Obstruction in a Cohort of Elite Cross-country Skiers. Med Sci Sports Exerc. 2021;53(6):1134-41.
55. Nielsen EW, Hull JH, Backer V. High prevalence of exercise-induced laryngeal obstruction in athletes. Med Sci Sports Exerc. 2013;45(11):2030-5.
56. Hull JH, Walsted ES, Pavitt MJ, Menzies-Gow A, Backer V, Sandhu G. High Prevalence of Laryngeal Obstruction during Exercise in Severe Asthma. American Journal of Respiratory and Critical Care Medicine. 2019;199(4):538-42.
57. McFadden ER, Zawadski DK. Vocal cord dysfunction masquerading as exercise-induced asthma. a physiologic cause for "choking" during athletic activities. American Journal of Respiratory and Critical Care Medicine. 1996;153(3):942-7.
58. Walsted ES, Hvedstrup J, Eiberg H, Backer V. Heredity of supraglottic exercise-induced laryngeal obstruction. European Respiratory Journal. 2017;50(2):1700423.
59. Benestad MR, Drageset J, Clemm H, Røksund OD, Vollsæter M, Halvorsen T, et al. Self-Reported Health in Adolescents With Exercise-Induced Laryngeal Obstruction; A Cross-Sectional Study. Frontiers in Pediatrics. 2021;Volume 9 - 2021.
60. Clemm HH, Olin JT, McIntosh C, Schwellnus M, Sewry N, Hull JH, et al. Exercise-induced laryngeal obstruction (EILO) in athletes: a narrative review by a subgroup of the IOC Consensus on 'acute respiratory illness in the athlete'. Br J Sports Med. 2022.
61. Røksund OD, Heimdal JH, Olofsson J, Maat RC, Halvorsen T. Larynx during exercise: the unexplored bottleneck of the airways. Eur Arch Otorhinolaryngol. 2015;272(9):2101-9.
62. Vollsæter M, Stensrud T, Maat R, Halvorsen T, Røksund OD, Sandnes A, et al. Exercise Related Respiratory Problems in the Young-Is It Exercise-Induced Bronchoconstriction or Laryngeal Obstruction? Front Pediatr. 2021;9:800073.
63. Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, et al. GINA 2019: a fundamental change in asthma management. European Respiratory Journal. 2019;53(6):1901046.

64. Pigakis KM, Stavrou VT, Pantazopoulos I, Daniil Z, Kontopodi AK, Gourgoulianis K. Exercise-Induced Bronchospasm in Elite Athletes. Cureus. 2022;14(1):e20898.
65. Sandnes A, Hilland M, Vollsæter M, Andersen T, Engesæter IØ, Sandvik L, et al. Severe Exercise-Induced Laryngeal Obstruction Treated With Supraglottoplasty. Frontiers in surgery. 2019;6:44-.
66. Knöpfli BH, Luke-Zeitoun M, von Duvillard SP, Burki A, Bachlechner C, Keller H. High incidence of exercise-induced bronchoconstriction in triathletes of the Swiss national team. Br J Sports Med. 2007;41(8):486-91; discussion 91.
67. Bougault V, Turmel J, Boulet LP. Airway hyperresponsiveness in elite swimmers: is it a transient phenomenon? J Allergy Clin Immunol. 2011;127(4):892-8.
68. Maat RC, Hilland M, Røksund OD, Halvorsen T, Olofsson J, Aarstad HJ, et al. Exercise-induced laryngeal obstruction: natural history and effect of surgical treatment. Eur Arch Otorhinolaryngol. 2011;268(10):1485-92.
69. Irewall T, Bäcklund C, Naumburg E, Ryding M, Stenfors N. A longitudinal follow-up of continuous laryngoscopy during exercise test scores in athletes irrespective of laryngeal obstruction, respiratory symptoms, and intervention. BMC Sports Science, Medicine and Rehabilitation. 2023;15(1):87.
70. Horváth I, Barnes PJ, Loukides S, Sterk PJ, Högman M, Olin A-C, et al. A European Respiratory Society technical standard: exhaled biomarkers in lung disease. European Respiratory Journal. 2017;49(4):1600965.
71. Buchvald F, Hermansen MN, Nielsen KG, Bisgaard H. Exhaled nitric oxide predicts exercise-induced bronchoconstriction in asthmatic school children. Chest. 2005;128(4):1964-7.
72. Schoos AM, Christiansen CF, Stokholm J, Bønnelykke K, Bisgaard H, Chawes BL. FeNO and Exercise Testing in Children at Risk of Asthma. J Allergy Clin Immunol Pract. 2018;6(3):855-62.e2.
73. Henriksen AH, Tveit KH, Holmen TL, Sue-Chu M, Bjermer L. A study of the association between exercise-induced wheeze and exercise versus methacholine-induced bronchoconstriction in adolescents. Pediatric Allergy and Immunology. 2002;13(3):203-8.
74. Johansson H, Norlander K, Alving K, Hedenström H, Janson C, Malinovschi A, et al. Exercise test using dry air in random adolescents: Temporal profile and predictors of bronchoconstriction. Respirology. 2016;21(2):289-96.
75. Dickinson J, Gowers W, Sturridge S, Williams N, Kippelen P, Simpson A, et al. Fractional exhaled nitric oxide in the assessment of exercise-induced bronchoconstriction: A multicenter retrospective analysis of UK-based athletes. Scand J Med Sci Sports. 2023;33(7):1221-30.
76. Decrue F, Gorlanova O, Usemann J, Frey U. Lung functional development and asthma trajectories. Seminars in Immunopathology. 2020;42(1):17-27.
77. McGeachie MJ, Yates KP, Zhou X, Guo F, Sternberg AL, Van Natta ML, et al. Patterns of Growth and Decline in Lung Function in Persistent Childhood Asthma. N Engl J Med. 2016;374(19):1842-52.
78. Koefoed HJL, Gehring U, Vonk JM, Koppelman GH. Blood eosinophils associate with reduced lung function growth in adolescent asthmatics. Clin Exp Allergy. 2021;51(4):556-63.
79. Meurs H, Gosens R, Zaagsma J. Airway hyperresponsiveness in asthma: lessons from in vitro model systems and animal models. European Respiratory Journal.32(2):487-502.

80. Hollams EM, Deverell M, Serralha M, Suriyaarachchi D, Parsons F, Zhang G, et al. Elucidation of asthma phenotypes in atopic teenagers through parallel immunophenotypic and clinical profiling. J Allergy Clin Immunol. 2009;124(3):463-70, 70.e1-16.
81. Harmsen L, Ulrik CS, Porsbjerg C, Thomsen SF, Holst C, Backer V. Airway hyperresponsiveness and development of lung function in adolescence and adulthood. Respir Med. 2014;108(5):752-7.
82. POSTMA DS, KOPPELMAN GH, MEYERS DA. The Genetics of Atopy and Airway Hyperresponsiveness. American Journal of Respiratory and Critical Care Medicine. 2000;162(supplement_2):S118-S23.
83. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, et al. Practical guide to skin prick tests in allergy to aeroallergens. Allergy. 2012;67(1):18-24.
84. Vidal C, Gude F, Boquete O, Fernández-Merino MC, Meijide LM, Rey J, et al. Evaluation of the phadiatop test in the diagnosis of allergic sensitization in a general adult population. J Investig Allergol Clin Immunol. 2005;15(2):124-30.
85. Crockcroft DW, Murdock KY, Berscheid BA. Relationship between atopy and bronchial responsiveness to histamine in a random population. Ann Allergy. 1984;53(1):26-9.
86. Peat JK, Britton WJ, Salome CM, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren. III. Effect of exposure to environmental allergens. Clin Allergy. 1987;17(4):291-300.
87. Backer V, Ulrik CS, Hansen KK, Laursen EM, Dirksen A, Bach-Mortensen N. Atopy and bronchial responsiveness in random population sample of 527 children and adolescents. Ann Allergy. 1992;69(2):116-22.
88. Burrows B, Sears MR, Flannery EM, Herbison GP, Holdaway MD. Relations of bronchial responsiveness to allergy skin test reactivity, lung function, respiratory symptoms, and diagnoses in thirteen-year-old New Zealand children. J Allergy Clin Immunol. 1995;95(2):548-56.
89. SEARS MR, BURROWS B, HERBISON GP, HOLDAWAY MD, FLANNERY EM. Atopy in childhood. II. Relationship to airway responsiveness, hay fever and asthma. Clinical & Experimental Allergy. 1993;23(11):949-56.
90. Caggiano S, Cutrera R, Di Marco A, Turchetta A. Exercise-Induced Bronchospasm and Allergy. Front Pediatr. 2017;5:131.
91. Carra S, Zhang H, Kurukulaaratchy RJ, Arshad SH. Natural History of Airway Hyperresponsiveness and Its Association With Asthma Traits. Allergy.n/a(n/a).
92. The European Community Respiratory Health Survey II. Main Questionnaire [Internet]. http://www.ecrhs.org/Quests.htm [updated 27/03/14.
93. Grassi M, Rezzani C, Biino G, Marinoni A. Asthma-like symptoms assessment through ECRHS screening questionnaire scoring. J Clin Epidemiol. 2003;56(3):238-47.
94. Johansson H, Emtner M, Janson C, Nordang L, Malinovschi A. The course of specific self-reported exercise-induced airway symptoms in adolescents with and without asthma. ERJ Open Research. 2020;6(4):00349-2020.
95. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.
96. Internet: Olink; 2025 [Available from: https://olink.com/products/olink-target-96.
97. Fox SM, 3rd, Naughton JP, Haskell WL. Physical activity and the prevention of coronary heart disease. Ann Clin Res. 1971;3(6):404-32.

98. Seccombe LM, Peters MJ, Buddle L, Farah CS. Exercise-Induced Bronchoconstriction Identified Using the Forced Oscillation Technique. Front Physiol. 2019;10:1411.
99. Maat RC, Roksund OD, Halvorsen T, Skadberg BT, Olofsson J, Ellingsen TA, et al. Audiovisual assessment of exercise-induced laryngeal obstruction: reliability and validity of observations. Eur Arch Otorhinolaryngol. 2009;266(12):1929-36.
100. Parsons JP, Kaeding C, Phillips G, Jarjoura D, Wadley G, Mastronarde JG. Prevalence of exercise-induced bronchospasm in a cohort of varsity college athletes. Med Sci Sports Exerc. 2007;39(9):1487-92.
101. Sunyer J, Pekkanen J, Garcia-Esteban R, Svanes C, Künzli N, Janson C, et al. Asthma score: predictive ability and risk factors. Allergy. 2007;62(2):142-8.
102. Kukafka DS, Lang DM, Porter S, Rogers J, Ciccolella D, Polansky M, et al. Exercise-induced Bronchospasm in High School Athletes via a Free Running Test: Incidence and Epidemiology. Chest. 1998;114(6):1613-22.
103. RUNDELL KW, IM J, MAYERS LB, WILBER RL, SZMEDRA L, SCHMITZ HR. Self-reported symptoms and exercise-induced asthma in the elite athlete. Medicine & Science in Sports & Exercise. 2001;33(2):208-13.
104. Parsons JP, Cosmar D, Phillips G, Kaeding C, Best TM, Mastronarde JG. Screening for exercise-induced bronchoconstriction in college athletes. J Asthma. 2012;49(2):153-7.
105. Romberg K, Tufvesson E, Bjermer L. Extended diagnostic criteria used for indirect challenge testing in elite asthmatic swimmers. Respiratory Medicine. 2012;106(1):15-24.
106. Scollo M, Zanconato S, Ongaro R, Zaramella C, Zacchello F, Baraldi E. Exhaled Nitric Oxide and Exercise-Induced Bronchoconstriction in Asthmatic Children. American Journal of Respiratory and Critical Care Medicine. 2000;161(3):1047-50.
107. Marchal F, Schweitzer C, Thuy LV. Forced oscillations, interrupter technique and body plethysmography in the preschool child. Paediatr Respir Rev. 2005;6(4):278-84.
108. Ducharme FM, Chan R. Oscillometry in the diagnosis, assessment, and monitoring of asthma in children and adults. Annals of Allergy, Asthma & Immunology. 2025;134(2):135-43.
109. Price OJ, Ansley L, Bikov A, Hull JH. The role of impulse oscillometry in detecting airway dysfunction in athletes. J Asthma. 2016;53(1):62-8.
110. Veneroni C, Pompilio PP, Alving K, Janson C, Nordang L, Dellacà R, et al. Self-reported exercise-induced dyspnea and airways obstruction assessed by oscillometry and spirometry in adolescents. Pediatr Allergy Immunol. 2022;33(1):e13702.
111. Barreto M, Veneroni C, Caiulo M, Evangelisti M, Pompilio PP, Mazzuca MC, et al. Within-breath oscillometry for identifying exercise-induced bronchoconstriction in pediatric patients reporting symptoms with exercise. Front Pediatr. 2023;11:1324413.
112. Evans TM, Rundell KW, Beck KC, Levine AM, Baumann JM. Impulse oscillometry is sensitive to bronchoconstriction after eucapnic voluntary hyperventilation or exercise. J Asthma. 2006;43(1):49-55.
113. Malmberg LP, Pelkonen AS, Mattila PS, Hammarén-Malmi S, Mäkelä MJ. Exhaled nitric oxide and exercise-induced bronchoconstriction in young wheezy children – interactions with atopy. Pediatric Allergy and Immunology. 2009;20(7):673-8.

114. Sverrild A, Porsbjerg C, Thomsen SF, Backer V. Airway hyperresponsiveness to mannitol and methacholine and exhaled nitric oxide: a random-sample population study. J Allergy Clin Immunol. 2010;126(5):952-8.
115. Qvarnström B, Engström G, Frantz S, Zhou X, Zaigham S, Sundström J, et al. Impulse oscillometry indices in relation to respiratory symptoms and spirometry in the Swedish Cardiopulmonary Bioimage Study. ERJ Open Res. 2023;9(5).
116. Abu-Hasan M, Tannous B, Weinberger M. Exercise-induced dyspnea in children and adolescents: if not asthma then what? Ann Allergy Asthma Immunol. 2005;94(3):366-71.
117. Jansrud Hammer I, Halvorsen T, Vollsæter M, Hilland M, Heimdal J-H, Røksund OD, et al. Conundrums in the breathless athlete; exercise-induced laryngeal obstruction or asthma? Scandinavian Journal of Medicine & Science in Sports. 2022;32(6):1041-9.
118. Carlsen PH, Muralitharan P, Fenne H, Hammer IJ, Engan M, Vollsæter M, et al. Laryngeal response to high-intensity exercise in healthy athletes. BMJ Open Sport Exerc Med. 2024;10(2):e001850.
119. Walsted ES, Famokunwa B, Andersen L, Rubak SL, Buchvald F, Pedersen L, et al. Characteristics and impact of exercise-induced laryngeal obstruction: an international perspective. ERJ Open Research. 2021;7(2):00195-2021.
120. Roksund OD, Maat RC, Heimdal JH, Olofsson J, Skadberg BT, Halvorsen T. Exercise induced dyspnea in the young. Larynx as the bottleneck of the airways. Respir Med. 2009;103(12):1911-8.
121. Siewers K, Backer V, Walsted ES. A systematic review of surgical treatment for supraglottic exercise-induced laryngeal obstruction. Laryngoscope Investig Otolaryngol. 2019;4(2):227-33.
122. Orbelo D, Cofer S, Pianosi P. Exertional Stridor: Differential Diagnosis, Investigation, and Treatment Based on Serial Exercise Tests With Flexible Transnasal Flexible Laryngoscopy. CHEST. 2014;145(3):566A.
123. Norlander K, Johansson H, Jansson C, Nordvall L, Nordang L. Surgical treatment is effective in severe cases of exercise-induced laryngeal obstruction: A follow-up study. Acta Otolaryngol. 2015;135(11):1152-9.
124. Förster R, Davalos-Misslitz AC, Rot A. CCR7 and its ligands: balancing immunity and tolerance. Nature Reviews Immunology. 2008;8(5):362-71.
125. Wang G, Hallberg J, Faner R, Koefoed HJ, Kebede Merid S, Klevebro S, et al. Plasticity of Individual Lung Function States from Childhood to Adulthood. Am J Respir Crit Care Med. 2023;207(4):406-15.
126. Yamashita N, Tashimo H, Matsuo Y, Ishida H, Yoshiura K, Sato K, et al. Role of CCL21 and CCL19 in allergic inflammation in the ovalbumin-specific murine asthmatic model. Journal of Allergy and Clinical Immunology. 2006;117(5):1040-6.
127. Kawakami M, Narumoto O, Matsuo Y, Horiguchi K, Horiguchi S, Yamashita N, et al. The role of CCR7 in allergic airway inflammation induced by house dust mite exposure. Cellular Immunology. 2012;275(1):24-32.
128. Kaur D, Saunders R, Berger P, Siddiqui S, Woodman L, Wardlaw A, et al. Airway smooth muscle and mast cell-derived CC chemokine ligand 19 mediate airway smooth muscle migration in asthma. Am J Respir Crit Care Med. 2006;174(11):1179-88.
129. Nakano K, Whitehead GS, Lyons-Cohen MR, Grimm SA, Wilkinson CL, Izumi G, et al. Chemokine CCL19 promotes type 2 T-cell differentiation and allergic airway inflammation. J Allergy Clin Immunol. 2024;153(2):487-502.e9.

130. Lundblad LK, Thompson-Figueroa J, Leclair T, Sullivan MJ, Poynter ME, Irvin CG, et al. Tumor necrosis factor-alpha overexpression in lung disease: a single cause behind a complex phenotype. Am J Respir Crit Care Med. 2005;171(12):1363-70.
131. Brightling C, Berry M, Amrani Y. Targeting TNF-α: A novel therapeutic approach for asthma. Journal of Allergy and Clinical Immunology. 2008;121(1):5-10.
132. Berry MA, Hargadon B, Shelley M, Parker D, Shaw DE, Green RH, et al. Evidence of a role of tumor necrosis factor alpha in refractory asthma. N Engl J Med. 2006;354(7):697-708.
133. Reiss TF, Hill JB, Harman E, Zhang J, Tanaka WK, Bronsky E, et al. Increased urinary excretion of LTE4 after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist. Thorax. 1997;52(12):1030.
134. Hallstrand TS, Moody MW, Wurfel MM, Schwartz LB, Henderson WR, Jr., Aitken ML. Inflammatory basis of exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 2005;172(6):679-86.
135. Carraro S, Corradi M, Zanconato S, Alinovi R, Pasquale MF, Zacchello F, et al. Exhaled breath condensate cysteinyl leukotrienes are increased in children with exercise-induced bronchoconstriction. Journal of Allergy and Clinical Immunology. 2005;115(4):764-70.
136. Kim KW, Lee KE, Kim ES, Song TW, Sohn MH, Kim K-E. Serum Eosinophil-Derived Neurotoxin (EDN) in Diagnosis and Evaluation of Severity and Bronchial Hyperresponsiveness in Childhood Asthma. Lung. 2007;185(2):97-103.
137. Anderson SD. Indirect Challenge Tests: Airway Hyperresponsiveness in Asthma: Its Measurement and Clinical Significance. Chest. 2010;138(2, Supplement):25S-30S.
138. Lúdvíksdóttir D, Janson C, Högman M, Hedenström H, Björnsson E, Boman G. Exhaled nitric oxide and its relationship to airway responsiveness and atopy in asthma. Respiratory Medicine. 1999;93(8):552-6.
139. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. Eur Respir J. 1995;8(3):483-91.
140. Sunyer J, Pekkanen J, Garcia-Esteban R, Svanes C, Künzli N, Janson C, et al. Asthma score: predictive ability and risk factors. Allergy. 2007;62(2):142-8.
141. Olin JT, Shaffer M, Nauman E, Durso CS, Fan EM, Staudenmayer H, et al. Development and validation of the Exercise-Induced Laryngeal Obstruction Dyspnea Index (EILODI). Journal of Allergy and Clinical Immunology. 2022;149(4):1437-44.
142. Rundell KW, Wilber RL, Szmedra L, Jenkinson DM, Mayers LB, Im J. Exercise-induced asthma screening of elite athletes: field versus laboratory exercise challenge. Med Sci Sports Exerc. 2000;32(2):309-16.
143. Ogston J, Butcher JD. A Sport-Specific Protocol for Diagnosing Exercise-Induced Asthma in Cross-Country Skiers. Clinical Journal of Sport Medicine. 2002;12(5):291-5.
144. Wilber RL, Rundell KW, Szmedra L, Jenkinson DM, Im J, Drake SD. Incidence of exercise-induced bronchospasm in Olympic winter sport athletes. Med Sci Sports Exerc. 2000;32(4):732-7.
145. Rundell KW, Slee JB. Exercise and other indirect challenges to demonstrate asthma or exercise-induced bronchoconstriction in athletes. Journal of Allergy and Clinical Immunology. 2008;122(2):238-46.

146. Carlsen KH, Engh G, Mørk M. Exercise-induced bronchoconstriction depends on exercise load. Respir Med. 2000;94(8):750-5.
147. Price OJ, Hull JH, Ansley L. Advances in the diagnosis of exercise-induced bronchoconstriction. Expert Review of Respiratory Medicine. 2014;8(2):209-20.
148. Anderson SD, Pearlman DS, Rundell KW, Perry CP, Boushey H, Sorkness CA, et al. Reproducibility of the airway response to an exercise protocol standardized for intensity, duration, and inspired air conditions, in subjects with symptoms suggestive of asthma. Respiratory Research. 2010;11(1):120.
149. Price OJ, Ansley L, Levai IK, Molphy J, Cullinan P, Dickinson JW, et al. Eucapnic Voluntary Hyperpnea Testing in Asymptomatic Athletes. American Journal of Respiratory and Critical Care Medicine. 2016;193(10):1178-80.
150. Jackson A, Allen H, Hull JH, Hopker J, Backhouse SH, Price OJ, et al. Diagnosing exercise-induced bronchoconstriction: Over-or under-detection? Allergy. 2020;75(2):460-3.
151. Olin JT, Clary MS, Fan EM, Johnston KL, State CM, Strand M, et al. Continuous laryngoscopy quantitates laryngeal behaviour in exercise and recovery. European Respiratory Journal. 2016;48(4):1192-200.
152. Tervonen H, Niskanen MM, Sovijärvi AR, Hakulinen AS, Vilkman EA, Aaltonen LM. Fiberoptic videolaryngoscopy during bicycle ergometry: a diagnostic tool for exercise-induced vocal cord dysfunction. Laryngoscope. 2009;119(9):1776-80.
153. Hull JH, Walsted ES, Orton CM, Williams P, Ward S, Pavitt MJ. Feasibility of portable continuous laryngoscopy during exercise testing. ERJ Open Res. 2019;5(1).
154. Mirza KK, Walsted ES, Backer V. Ergospirometry with concurrent fibre optic laryngoscopy: a randomised crossover study. Eur Clin Respir J. 2017;4(1):1399033.
155. Walsted ES, Hull JH, Hvedstrup J, Maat RC, Backer V. Validity and reliability of grade scoring in the diagnosis of exercise-induced laryngeal obstruction. ERJ Open Research. 2017;3(3):00070-2017.
156. Norlander K, Christensen PM, Maat RC, Halvorsen T, Heimdal JH, Morén S, et al. Comparison between two assessment methods for exercise-induced laryngeal obstructions. Eur Arch Otorhinolaryngol. 2016;273(2):425-30.
157. Mæstad R, Hanan A, Kristian Kvidaland H, Clemm H, Arghandeh R. LarynxFormer: a transformer-based framework for processing and segmenting laryngeal images. Front Digit Health. 2025;7:1459136.
158. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med. 2011;184(5):602-15.
159. Gemicioglu B, Musellim B, Dogan I, Guven K. Fractional exhaled nitric oxide (FeNo) in different asthma phenotypes. Allergy Rhinol (Providence). 2014;5(3):157-61.
160. Torén K, Murgia N, Schiöler L, Bake B, Olin AC. Reference values of fractional excretion of exhaled nitric oxide among non-smokers and current smokers. BMC Pulm Med. 2017;17(1):118.

Acta Universitatis Upsaliensis

Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 2205

Editor: The Dean of the Faculty of Medicine

A doctoral dissertation from the Faculty of Medicine, Uppsala University, is usually a summary of a number of papers. A few copies of the complete dissertation are kept at major Swedish research libraries, while the summary alone is distributed internationally through the series Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine. (Prior to January, 2005, the series was published under the title "Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine".)

Distribution: publications.uu.se
urn:nbn:se:uu:diva-568684

ACTA UNIVERSITATIS
UPSALIENSIS
2025