Exercise induced breathing problems in adolescents

HENRIK JOHANSSON
Abstract


Experiencing respiratory symptoms in conjunction with exercise is common in children and adolescents and can have a negative impact on daily life. The aim of the thesis was to estimate the prevalence of exercise-induced dyspnoea, exercise-induced bronchoconstriction (EIB) and exercise-induced laryngeal obstruction (E-ILO) in a general adolescent population, and to explore factors associated with EIB.

Methods: All 12-13-year-old adolescents in the city of Uppsala (n=3,838) participated in a survey on exercise-induced dyspnoea. A subsample of adolescents who answered the survey, 103 randomly selected adolescents reporting exercise-induced dyspnoea and 47 random adolescents who did not report exercise-induced dyspnoea underwent standardised treadmill exercise tests for EIB and E-ILO. The exercise test for EIB was performed while breathing dry air; a positive test was defined as a decrease ≥10% in FEV$_1$ from baseline. E-ILO was investigated using continuous laryngoscopy during exercise. Health related quality of life (HRQoL), and objectively measured daily physical activity were investigated in those with (n=49) and without (n=91) a positive EIB-test.

Results: The prevalence of exercise-induced dyspnoea was 14%, and the estimated prevalence of EIB and E-ILO in the total population was 19.2% and of 5.7%, respectively, with no gender differences. In adolescents with exercise-induced dyspnoea 40% had EIB, 6% had E-ILO, and 5% had both conditions.

An increased baseline level of fraction of nitric oxide in exhaled air (FeNO), female gender, and exercise-induced dyspnoea were associated with a positive EIB test. Female adolescents with EIB had lower HRQoL and lower baseline lung function compared to females without EIB. These differences were not observed in male adolescents. There was no difference in time spent in moderate- to vigorous daily physical activity between adolescents with and without EIB.

Keywords: Exercise, dyspnoea, bronchoconstriction, laryngeal obstruction, adolescents, HRQoL, physical activity

Henrik Johansson, Department of Neuroscience, Physiotherapy, Box 593, Uppsala University, SE-751 24 UPPSALA, Sweden.

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List of Papers

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


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<th>Full Form</th>
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<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
</tr>
<tr>
<td>CLE</td>
<td>Continuous laryngoscopy exercise test</td>
</tr>
<tr>
<td>EIB</td>
<td>Exercise-induced bronchoconstriction</td>
</tr>
<tr>
<td>E-ILO</td>
<td>Exercise-induced laryngeal obstruction</td>
</tr>
<tr>
<td>ERS</td>
<td>European Respiratory Society</td>
</tr>
<tr>
<td>FeNO</td>
<td>Fraction of nitric oxide (NO) in exhaled air</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Forced expiratory volume in 1 second</td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; % pred.</td>
<td>The FEV&lt;sub&gt;1&lt;/sub&gt; expressed in percent of predicted value</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced Vital Capacity</td>
</tr>
<tr>
<td>FVC % pred</td>
<td>The FVC expressed in percent of predicted value</td>
</tr>
<tr>
<td>HAD</td>
<td>Hospital anxiety and depression scale</td>
</tr>
<tr>
<td>HRQoL</td>
<td>Health related quality of life</td>
</tr>
<tr>
<td>ICS</td>
<td>Inhaled corticosteroids</td>
</tr>
<tr>
<td>IgE</td>
<td>Immunoglobulin E</td>
</tr>
<tr>
<td>LABA</td>
<td>Long acting bronchodilator agent</td>
</tr>
<tr>
<td>LTRA</td>
<td>Leukotriene receptor antagonist</td>
</tr>
<tr>
<td>PedsQL</td>
<td>Pediatric Quality of Life Inventory</td>
</tr>
<tr>
<td>PEFR</td>
<td>Peak expiratory flow rate</td>
</tr>
<tr>
<td>SABA</td>
<td>Short acting bronchodilator agent</td>
</tr>
<tr>
<td>VCD</td>
<td>Vocal cord dysfunction</td>
</tr>
<tr>
<td>WHO</td>
<td>World health organisation</td>
</tr>
</tbody>
</table>
Introduction

Experiencing respiratory symptoms in conjunction with exercise (hereafter referred to as exercise-induced dyspnoea) is common in children and adolescents (1) and can have a negative impact on daily life (2-4). Although exercise-induced dyspnoea is reported to be common, prospective studies investigating its prevalence in the general adolescent population are rare, and its origins have not been fully investigated or understood (5, 6). In adolescents, exercise-induced bronchoconstriction (EIB), as an expression of asthma, is the most widely studied cause of exercise-induced dyspnoea. EIB is reported to be under-, over- and misdiagnosed in part due to the poor correlation between the degree of airway obstruction and the sensation of dyspnoea (7, 8). As such, a diagnosis should not be based on symptoms alone because symptoms lack sensitivity and specificity. Thus, the need for standardised testing has been emphasized in the literature (9, 10).

Another less common reason for experiencing exercise-induced dyspnoea is exercise-induced laryngeal obstruction (E-ILO), which is known to mimic EIB (11). Little data on the prevalence of E-ILO has been reported (12, 13). To minimise morbidity and to be able to offer appropriate treatment options, subjects with exercise-induced dyspnoea must to be identified and diagnosed.

The challenge goals of this thesis were to contribute to current knowledge regarding the prevalence of exercise-induced dyspnoea in a general adolescent population, to investigate the prevalence of EIB and E-ILO using standardised exercise challenge tests, and to study the variables associated with and the consequences of EIB in adolescents.
Background

Exercise-induced dyspnoea

Exercise-induced dyspnoea indicates dyspnoea that occurs or worsens during physical activity. It is a common symptom in numerous medical disorders. EIB is the most widely studied cause of exercise-induced dyspnoea (14). Obstruction of the larynx during exercise, known as exercise-induced laryngeal obstruction (E-ILO) can also cause respiratory problems (15-17). This group of conditions has been increasingly recognized during recent years (18). Other conditions that might result in exercise-induced breathing problems are cardiac and respiratory conditions such as congestive heart disease, pulmonary embolism, bronchiectasis and cystic fibrosis (19).

When asked people describe dyspnoea in different ways, including, “I get tired easily”, “I cannot take a deep breath”, “my chest gets tight”, “my throat gets tight” or just “I get short of breath”. Experiencing respiratory problems in conjunction with exercise can have a negative impact on daily life. It can impair health related quality of life, and cause absence from school, sleep disturbances and activity limitations (2, 3, 20). Thus, dyspnoea during exercise is a symptom that warrants investigation especially in subjects who otherwise have no known lung or heart disease (7). Studies investigating the prevalence of exercise-induced dyspnoea in the general adolescent population are rare (1, 21).

Exercise-induced bronchoconstriction, EIB

EIB is defined as the acute transient narrowing of the lower airways after exercise in the presence or absence of clinically recognized asthma. The symptoms of EIB include cough, wheeze, chest tightness, shortness of breath, dyspnoea, excessive mucous production or feeling out of shape when the patient is actually in good physical condition (14). In persons with asthma EIB is among the first symptoms to appear, and it is typically the last symptom to disappear with treatment (22). Those with severe or poorly controlled asthma are more likely to manifest EIB than patients with less severe or well-controlled asthma (15).
It is not the exercise itself that is responsible for the narrowing of the airway. It is the increased ventilatory demand in conjunction with exercise. There are two main hypotheses regarding how water and heat loss might cause airways to narrow. In the most widely accepted osmotic hypothesis, dehydration leads to the increased osmolarity of the airway surface which in turn induce degranulation of airway mast cells and the release of chemical mediators of bronchoconstriction of the airways (23, 24). In the thermal hypothesis, EIB is a vascular event that involves vasoconstriction from airway cooling during exercise, which is followed by a reactive hyperaemia resulting in bronchial edema and plasma exudation (25).

To confirm the diagnosis of EIB standardized testing utilizing spirometry is suggested (9, 14, 26, 27). The diagnosis should not be made on symptoms alone, as symptoms associated with EIB lack sensitivity and specificity (28).

Diagnostic challenges come in two types, direct or indirect. A direct challenge is one in which pharmaceutical agents such as methacholine or histamine are provoking agents that act directly on smooth muscle. An indirect challenge is performed either as an exercise challenge test or a surrogate to exercise, such as eucapnic voluntary hyperpnoea or inhalation of mannitol or hypertonic saline (14). According to the American Thoracic Society (ATS) and the European Respiratory Society (ERS) EIB is best established by analysing changes in lung function after a specific exercise challenge. A fall in forced expiratory volume in one second (FEV₁) ≥ 10% is suggested as the diagnostic criteria for EIB (9, 29).

Currently, the most important determinants of EIB severity have been reported to be the water content of the inspired air and the level of ventilation achieved and sustained during exercise. Therefore, to increase the likelihood of a positive response in a susceptible person the recommended exercise protocol involves a rapid increase in exercise intensity over approximately 2–4 minutes to achieve high ventilation, which corresponds to a ventilation of 17.5–21 times the baseline FEV₁ or 80–90% of predicted maximal heart rate. Once the level has been attained the exercise should continue for another 4–6 minutes. During the test the subject should breathe dry air (<10 mg H₂O/L) with a nose clip in place. The exercise performed should be running or cycling, but running is preferred because a higher intensity is more rapidly achieved with running than with cycling (9). FEV₁ should be measured at baseline (before the exercise challenge) and at 5, 10, 15 and 30 minutes after exercise. Free running has been used to screen for EIB in population based studies because of its ease of administration (26, 30, 31). However, because the magnitude of EIB is influenced by environmental conditions and exercise load, standardised laboratory exercise challenge tests that have high specificity and sensitivity are recommended (14, 32).

EIB occurs in individuals with and without asthma. Its prevalence varies depending on the population under study and the diagnostic method. It is highly prevalent in children and adolescents that have been diagnosed with
asthma, in whom its prevalence has been reported to be between 40 to 60% (33-36). The reported prevalence of EIB in the general population of older children and adolescents varies. In the general population of 7-10-year-old subjects the prevalence of EIB was 7% when using the six-minute free running test (6MFRT) and a ≥ 15% fall in peak expiratory flow rate (PEFR) is used as a diagnostic criteria (37). When the same exercise challenge was used in a general population of 10-12 and 11-17-year-old children the prevalence was found to be 9% and 10%, respectively (26, 38). Among Spanish school children (13-14 years old) performing the 6MFRT the prevalence of EIB was 11% and the prevalence in a general group of 10-15-year-old Algerian children was 16% (28, 33). Studies investigating the prevalence of EIB in the general adolescent population using standardised exercise tests are rare. But in a Norwegian birth cohort of 10-year-old children a prevalence of almost 9% was reported when a standardised laboratory treadmill exercise challenge test was used (39).

Exercise-induced laryngeal obstruction, E-ILO

Inducible laryngeal obstruction (ILO) that causes breathing problems is a new consensus term that includes disorders known in the literature, such as vocal cord dysfunction (VCD), paradoxical vocal fold movement, and induced laryngomalacia among others (18). With the use of a prefix, a specific trigger to the umbrella term ILO is pointed out.

Exercise-induced laryngeal obstructions (E-ILO) consist of a group of conditions in which airflow is hampered at the laryngeal level during exercise, but not at rest. This group includes vocal cord dysfunction (VCD), which is the result of an abnormal adduction of the vocal cords during inspiration and supraglottic obstruction caused by collapsing of the aryepiglottic fold while the vocal cord motion is normal (18). In E-ILO, the onset of breathing difficulties peaks during exercise rather than after exercise and its symptoms such as throat tightness, dyspnoea and inspiratory stridor usually resolve within five minutes after discontinuation of exercise (14, 40, 41). There is currently no unifying hypothesis regarding the specific mechanism underlying the common pathways of exercise-induced glottic adduction and supraglottic narrowing.

E-ILO is diagnosed in a continuous laryngoscopy exercise test (CLE test) that assesses the dynamic behaviour of anatomical structures in the larynx from rest to exhaustion (42).

The larynx is filmed continuously and the laryngeal findings at the glottic and supraglottic levels are graded and scored according to the criteria described by Maat et al (17). The degrees of glottic adduction and medial rotation of the aryepiglottic folds are assessed on a scale of 0-3, where high scores indicate more obstruction.
Figures related to the prevalence of these conditions are uncertain due to heterogeneity in the terminology, diagnostic techniques and criteria (18). E-ILO was found to be the underlying disorder in 15% of active duty members of the US military presented with exercise-induced dyspnoea when the spirometry was used as the diagnostic method (43). In a retrospective study of well-trained athletes who were referred for asthma workup, 35% of the subjects were diagnosed with E-ILO when a CLE-test was used (13). In the general population only one prospective study has investigated the prevalence of E-ILO using a standardised exercise challenge and this study reported that E-ILO occurred in 7.5% of subjects aged 14-24 years old (12). E-ILO is reported to affect twice as many females as males (44). The coexistence of E-ILO and EIB has been described in case reports (45).

Health related quality of life (HRQoL) and anxiety and depression

HRQoL is considered a clinically important patient rated perceived effects of a disease, condition, illness, injury or treatment on various health domains (e.g., physical, emotional and social) (46). In the general population female adolescents report lower HRQoL than males (47). Adolescents with dyspnoea secondary to exercise report lower HRQoL than healthy peers, a finding that is evident in subjects both with and without asthma (2). Children and adolescents with asthma have impaired HRQoL compared to controls (48) and coexistence with EIB causes even greater impairment in HRQoL (49). The prevalence of anxiety and depressive symptoms are reported to be higher in adolescents with asthma than in those without asthma (50). The relationship between anxiety and depression and EIB has specifically not been investigated in adolescents with EIB and studies investigating gender differences in HRQoL and anxiety and depression are sparse.

Physical activity

Physical activity is defined as a set of behaviours that encompasses bodily movement produced by skeletal muscles that result in energy expenditure (51). Recommendations for appropriate amounts physical activity for the paediatric population have been developed, and international guidelines recommend at least 60 minutes of moderate to vigorous physical activity per day, seven days per week. (52).

Physical activity can be measured using indirect and direct measures. The most common way to measure physical activity at the population based level is through self-reports using indirect measures, including questionnaires,
diaries, surveys and interviews (53). Direct measures include double labelled water, calorimetry, physiologic markers (i.e., heart- or respiratory rates), motion sensors or direct observations.

Several studies have demonstrated reduced levels of physical activity in children with asthma compared to healthy peers (54, 55). In contrast other studies have not found such a difference (56, 57). The association between EIB and daily levels physical activity level in the general population has not been studied.

Predictors of EIB

Considering that the diagnosis of EIB should not be made based on symptoms alone and that standardised exercise tests can be unpractical, expensive and time-consuming, identifying variables that can be associated with EIB might be clinically valuable. Exhaled nitric oxide has been associated with EIB in asthmatic children, but these values have been reported to be more useful as a means of excluding rather than of confirming EIB (58). Whether this is also true also in the general adolescent population has not been investigated, and comparisons with other predictors are scarce (58).

Rationale for this thesis

Experiencing undiagnosed exercise-induced dyspnoea can have negative effects on daily life. Although it is common among adolescents, the reasons for experiencing exercise-induced dyspnoea are not fully understood. The most well-studied reason for exercise-induced dyspnoea is EIB. Another less common reason is E-ILO, which encompasses a group of conditions that involve the vocal cords and supraglottic structures in the larynx and wherein airflow in the larynx is hampered during physical exertion.

Because symptoms-based diagnosis is imprecise objective diagnostic tests are recommended for both EIB and E-ILO. Although thoroughly investigated in the asthmatic population, the prevalence of EIB in the adolescent general population using objective measures has not been analysed, and studies investigating factors associated with EIB are rare. The prevalence of E-ILO, in the general adolescent population has not been studied. A standardised exercise test with inhalation of dry air is recommended (in international guidelines) to confirm the diagnosis of EIB but the reaction to such a test protocol in the general population have not been described.
The overall aim of this thesis is to estimate the prevalence of exercise-induced dyspnoea and subsequently EIB and E-ILO in the general adolescent population and to specifically investigate factors associated with EIB.

**Specific aims**

- to investigate the prevalence of self-reported exercise-induced dyspnoea in the general adolescent population (Study I)

- to investigate the prevalence of EIB and E-ILO, using standardized exercise tests, in adolescents with and without self-reported exercise-induced dyspnoea (Study II)

- to study the temporal aspect of decline in FEV₁ after an EIB test with dry air ventilation in adolescents with and without EIB (Study III)

- to study variables that contribute to the presence of exercise-induced dyspnoea and EIB (Studies I and III)

- to describe and compare symptoms in the general adolescent population with and without self-reported exercise-induced dyspnoea (Study I)

- to describe and compare self-reported exercise induced respiratory symptoms in adolescents with EIB, E-ILO or exercise-induced dyspnoea without a diagnosis (Study II)

- to describe and compare HRQoL, anxiety and depression, and symptoms, in a population of adolescents with and without EIB, and to investigate gender differences (Study II-IV)

- to assess daily levels of physical activity in adolescents with and without self-reported exercise-induced dyspnoea and EIB (Studies I and IV)
Methods

Design and ethics
This thesis consists of four studies (table 1). In Study I all adolescents in Uppsala who were born in 1997-98 (n=3,838) were invited to participate in a survey. In Studies II – IV a subsample of adolescents who answered the survey participated, 103 randomly selected adolescents reporting exercise-induced dyspnoea and 47 random adolescents who did not report exercise-induced dyspnoea. The regional Ethical Review Board in Uppsala, Sweden approved the studies (Study I Dnr: 2010/272, Studies II-IV Dnr: 2011/413). Participating adolescents and their guardians were given written and verbal information about the study and informed consent was obtained from each participating adolescent and their guardian. The study design, sample size, and type of data collected are presented in table 1.
Table 1. Overview of sample sizes, study design, and type of data collected in studies included in the thesis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Design</th>
<th>Type of Data Collected</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>n=3,838</td>
<td>Observational/cross sectional</td>
<td>Questionnaire (exercise-induced dyspnoea, asthma, self-reported physical activity)</td>
</tr>
<tr>
<td>II</td>
<td>n=150</td>
<td>Observational (Descriptive, correlative)</td>
<td>Exercise tests to diagnose EIB and E-ILO</td>
</tr>
<tr>
<td>III</td>
<td>n=146</td>
<td>Observational (Descriptive, correlative)</td>
<td>Lung function reaction after exercise test, biomarkers</td>
</tr>
<tr>
<td>IV</td>
<td>n=140</td>
<td>Observational (Descriptive, correlative)</td>
<td>Questionnaire (HRQoL, anxiety and depression), objectively measured physical activity</td>
</tr>
</tbody>
</table>

EIB= exercise-induced bronchoconstriction, E-ILO= exercise-induced laryngeal obstruction, HRQoL= health related quality of life

Participants and procedures

Characteristics of the study samples are presented in table 2.

Table 2. Characteristics of adolescents included in the thesis. Numbers are mean and standard deviations or proportions unless otherwise stated.

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants and procedures</th>
<th>Characteristics</th>
<th>Study I (n=2,309)</th>
<th>Study II (n=103 exercise-induced dyspnoea)</th>
<th>Study III (n=47 Control)</th>
<th>Study IV (n=91 EIB)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age (years, min, max)</td>
<td>13.1 (12,14)</td>
<td>14.2 (13,15)</td>
<td>14.2 (13,15)</td>
<td>14.2 (13,15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Females (n,%)</td>
<td>1136 (49.2)</td>
<td>62 (62.6)</td>
<td>26 (55.3)</td>
<td>36 (73.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BMI (kg/m²)</td>
<td>19.4±2.9</td>
<td>21.1±2.8</td>
<td>20.9±2.9</td>
<td>21.3±2.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asthma</td>
<td>338 (14.6)</td>
<td>43 (41.7)</td>
<td>2 (4.3)</td>
<td>22 (44.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FEV₁ % pred (%)</td>
<td>-</td>
<td>92.0±10.6</td>
<td>93.5±9.2</td>
<td>90.3±9.4</td>
</tr>
</tbody>
</table>

BMI= body mass index, FEV₁= forced expiratory volume in one second
Study I

Participants
All 12-13-year-old adolescents (born in 1997-98) in the city of Uppsala (n=3,838) were invited to participate. Addresses for all adolescents were collected from the Swedish Population Register.

Procedures
A letter was sent to adolescents and parents with an offer to participate in the study. Parents, together with their child, were asked to complete an online self-administered questionnaire. A reminder was sent to adolescents who did not respond within four weeks. If necessary a reminder together with a paper copy of the questionnaire and an enclosed stamped self-addressed return envelope was sent one month later. Data were collected from January to May 2011.

Out of the 3,838 questionnaires, 23 were returned unopened due to incorrect addresses. The response rate was 64.3% leaving a total of 2,468 questionnaires eligible for analysis. One hundred and fifty-nine adolescents declared that they did not want to participate in the study, thus the final study population comprised 2,309 adolescents (60.2%) (1,136 females) (table 2). A total of 1,399 adolescents answered the questionnaire online and the rest (n = 910) filled out and returned a paper copy. There were no differences regarding age, gender and postal area codes between responders and non-responders.

Studies II-IV

Participants
All responders in Study I (n=2,309, by now 13 to 15 years old) were divided into two separate lists according to their answer to the question “Have you had an attack of shortness of breath that came following strenuous activity at any time, in the last 12 months?”

After stratifying for gender according to the results of Study I (females-males ratio 3:2) one randomly ordered list was created for adolescents with a positive answer (n=330, exercise-induced dyspnoea) and another was created for adolescents with a negative answer (n=1979, controls) (figure 1). Following this list, the guardians of the adolescents were contacted by phone by HJ, informed of the study and asked if they were willing to receive detailed information via e-mail (targeted to both adults and adolescents) about the study. They were also asked if they were willing to receive a call from a research nurse in approximately seven days to ask about their participation in the study. The exclusion criteria were pulmonary disease unrelated to asthma, cardiac co-morbidity or a functional disability that resulted in the inabil-
ity to perform exercise tests. The first 103 adolescents with exercise-induced dyspnoea and the first 47 controls who agreed to participate were recruited for the clinical part of this research (figure 1, table 3).

Figure 1. Adolescents’ inclusion and exclusion. HRQoL; Health related quality of life, FeNO; fraction exhaled nitric oxide, EIB; exercise-induced bronchoconstriction; CLE, continuous laryngoscopy exercise test
Procedures

The adolescents were invited to three clinical visits.

First clinical visit
At the first visit, which was conducted by a research nurse, the adolescents were informed about the study protocol and they gave written informed consent. The adolescents were then interviewed about asthma and medication, and they completed questionnaires regarding HRQoL and anxiety and depression. Height, weight and fractional exhaled nitric oxide (FeNO) were measured and venous blood samples for analyses of IgE sensitisation and eosinophil cationic protein (ECP) were collected. The adolescents were instructed (via verbal and written information) on how to prepare for the two coming exercise tests.

Second clinical visit
The second visit consisted of a standardised exercise challenge test on a treadmill with inhalation of dry air to detect EIB (14). The EIB test was performed on average a median (IQR) of 12 (6-19) days after the first visit. The investigator (HJ) who collected the data was blinded to whether the adolescents belonged to the exercise-induced dyspnoea group or the control group. Following the EIB test, the adolescents were instructed to use an accelerometer to assess physical activity for seven days. Following the seven-day period, the monitors were collected (the adolescents were given a prepaid envelope in which to return the monitor), and the data were downloaded and archived.

Third clinical visit
The third visit consisted of a standardised exercise challenge test on a treadmill using continuous filming of the larynx with a laryngoscope to detect E-ILO (CLE test). The CLE test was performed on average a median (IQR) of 38 (22-66) days after the second visit. The investigator (KN) who collected the data was blinded to whether the adolescents belonged to the exercise-induced dyspnoea group or the control group and to the results from the EIB tests performed during visit two.

Adolescents declining participation (Studies II-IV)
A total of 199 adolescents with exercise-induced dyspnoea were contacted. Of these, 96 adolescents declined participation. A total of 123 control adolescents were contacted. Of these, 76 adolescents declined participation (figure 1). The characteristics of the participating adolescents and the adolescents declining participation are presented in table 3.
Table 3. Characteristics of participating adolescents and adolescents declining participation in study II. Results are presented as mean ±SD and number, n (%)

<table>
<thead>
<tr>
<th>Answers from questionnaire study I</th>
<th>Exercise-induced dyspnoea</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participating adolescents</td>
<td>Declining participation</td>
</tr>
<tr>
<td>Age</td>
<td>13.7±0.66</td>
<td>13.7±0.66</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.4 ±2.6</td>
<td>19.4 ±2.8</td>
</tr>
<tr>
<td>Asthma</td>
<td>43 (41.7)</td>
<td>27 (28.1)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>29 (28.3)</td>
<td>30 (31.3)</td>
</tr>
<tr>
<td>Current wheeze</td>
<td>57 (55.3)</td>
<td>47 (49)</td>
</tr>
<tr>
<td>Day time dyspnoea</td>
<td>17 (16.5)</td>
<td>9 (9.4)</td>
</tr>
<tr>
<td>Nocturnal dyspnoea</td>
<td>27 (26.2)</td>
<td>20 (20.8)</td>
</tr>
<tr>
<td>Absence from school</td>
<td>15 (14.5)</td>
<td>17 (17.7)</td>
</tr>
</tbody>
</table>

BMI= body mass index

Four adolescents with exercise-induced dyspnoea declined participation in the exercise tests leaving 146 adolescents (99 with exercise-induced dyspnoea and 47 healthy controls) who performed the EIB test (figure 1). Of these 146 adolescents, 136 successfully completed the six minute exercise challenge test (figure 1). The reason that some adolescents did not complete the test was that they experienced breathing difficulties during the exercise provocation. However, lung function measurements were performed according to protocol on all adolescents and four of these adolescents had a FEV₁-fall ≥10% and were therefore defined as having EIB. The remaining six adolescents who did not complete the exercise challenge were not included in further analysis.

Another 19 adolescents (including 14 adolescents with exercise-induced dyspnoea) declined participation in the CLE test (figure 1). Another two adolescents were excluded at the time of the test; one was excluded due to equipment failure during the test and one subject was excluded due to fainting before the exercise challenge when the laryngoscope was inserted. In total 125 adolescents (83 with exercise-induced dyspnoea and 42 healthy controls) performed the exercise challenge test to detect E-ILO (figure 1).

Accelerometer data for 16 adolescents were excluded because of quality criteria were not fulfilled according to the protocol. Thus, leaving data from 130 adolescents for analysis (figure 1).
Data collection

Questionnaire (Study I)

In the questionnaire (appendix 1) the variables were assessed with the following questions:

*Exercise-induced dyspnoea*: “Have you had an attack of shortness of breath that happened after strenuous activity at any time during the last 12 months?” (59)

*The diagnosis of ever asthma*: “Have you ever been diagnosed by a physician as having asthma.”

*Rhinitis*: “Have you ever had hay fever?” (60).

*Current wheeze*: "Have you had wheezing or whistling in the chest during the last 12 months?" (60).

*Daytime dyspnoea*: "Have you had an attack of shortness of breath that came on during the day when you were at rest at any time during the last 12 months?" (60).

*Nocturnal dyspnoea*: "Have you woken up with a feeling of tightness in the chest at any time during the last 12 months?" and/or “Have you been woken by an attack of shortness of breath at any time during the last 12 months?" (60).

*Exercise induced respiratory symptoms* “Have you had any of the following symptoms during or following physical exercise, more than once, in the last 12 months; wheeze, chest tightness, cough, throat tightness, choking sensation, hoarseness or inspiratory stridor?”

*Absence from school*: Having missed ≥10 school days the last semester (i.e. five months period) because of infections or symptoms from the airways.

*Physical activity*: “During a typical or usual week, on how many days were you physically active for a total of at least 60 minutes per day? Physical activity is defined as all activities (school activities, transport to and from school and leisure activities) that raises your heart rate and makes you breathe hard" (61, 62). Adolescents that reported physical activity on at least a moderate level ≥ 60 minutes per day, 7 days per week were defined as being physically active according to international guidelines for children and adolescents (63, 64).
Medication: The use of inhaled corticosteroids (ICS), short-acting β₂-agonists (SABA), long-acting β₂-agonists (LABA), and leukotriene receptor antagonists (LTRA) in the past three months was recorded.

EIB test (Studies II-IV)
The adolescents were instructed to withdraw SABA at 8 h, LABA at 24 h and LTRA at 72 h prior to the test. The adolescents were instructed not to use ICS on the day of the test and to avoid vigorous exercise, heavy meals, caffeine-containing foods or beverages and nicotine within the 4 h prior to the test.

Baseline spirometry was performed according to ATS/ERS guidelines (65), and the pre-challenge FEV₁ and forced vital capacity (FVC) were documented as the best of three measurements (Cardio Perfect dynamic spirometry, Welch Allyn, Höganäs, Sweden). FEV₁ and FVC were expressed as percent of the predicted value (66). During the EIB test on a treadmill (GE Marquette Series 2000 Treadmill, Waukesha WI, USA), the subject wore a nose clip and breathed through a tube (Aiolos Asthma test, Aiolos Medical AB, Karlstad, Sweden) that was connected to a central gas container of dry air (H₂O/L < 5 mg/L, 18 to 22°C). Heart rate was continuously assessed using a heart monitor (The CASE Exercise Testing System, GE Medical Systems, Milwaukee WI; USA). The end-point was achieved when the cardiac frequency was increased to 90% of the predicted maximum ((208 - (0.7 x age)) x 0.9)) (67) within the first 1.5 min and was maintained throughout the 6-minute test by adjusting the treadmill speed and slope. FEV₁ was measured 5, 10, 15 and 30 min after the test. The best FEV₁ of two measurements at each time point was documented. EIB was defined as a fall in FEV₁ ≥10% from baseline at least at one time point within 30 min after the test (9). Adolescents who showed a decline in FEV₁ > 30% from baseline and experienced breathing problems within 15 min after exercise were offered nebulised salbutamol.

CLE test (Study II)
The adolescents were previously informed that there were no restrictions regarding asthma medication. Hence, those who usually took asthma medication before physical exercise should also do so before the CLE test. The adolescents were instructed to avoid vigorous exercise, heavy meals, caffeine-containing foods or beverages and nicotine within the 4 h prior to the test.

The CLE test was performed according to the method described by Heimdal et al (42). Before the test, Naphazoline-lidocaine was sprayed twice into each nostril to achieve local anaesthetic effect and dilatation. The participant warmed up on the treadmill at 10 km/h for 2 minutes (Master fitness
T590, Guangzhou, China). The treadmill was then stopped and a fiberoptic laryngoscope (Olympus ENF-P3, Southend-on-Sea, UK) was inserted into one nostril. The tip of the laryngoscope was placed just above the epiglottis where it provided a detailed view of the larynx. The laryngoscope was fastened in a specially designed helmet to stay in position and was connected to a camera (Ubicam, Sopro imaging, La Ciotat, France). The participant was equipped with a heart rate monitor consisting of a chest strap and wrist watch (T31, Polar, Oulu, Finland).

The participant started running at a speed of 9 km/h with no inclination, and the speed was increased by 1 km/h every minute until it reached 13 km/h. Thereafter the inclination was increased by 2% every minute. The adolescents were instructed to run until breathing problems forced them to stop, or, if no breathing problems occurred, until exhaustion. For the test to be considered successful, the heart rate had to reach ≥90% of the predicted maximum (67). The larynx was filmed continuously during the test and the larynx findings were graded immediately after the test according to the criteria described by Maat et al. (17). An obstruction grade of two or more at either the supraglottic or the glottic level, or both, was considered to be a positive response and was defined as E-ILO (17).

Fraction of nitric oxide (NO) in exhaled air (FeNO) (Study III)

FeNO was measured according to ATS/ERS recommendations (68), at 50 mL/s using a chemiluminescence NO analyser (NIOX Flex, Aerocrine AB, Solna, Sweden). The adolescents were instructed to avoid physical exercise and nitrate-rich food on the morning of the measurement day.

Health-related quality of life (Study IV)

The adolescents were asked to complete the teen version (ages 13 to 18 years old) of the Pediatric Quality of Life Inventory Generic Core Scales instrument (PedsQL™ version 4.0) (69). The PedsQL is a 23-items scale that covers the five following health domains: physical function, emotional function, social function, school function and general well-being. The instrument yields three summary scores, as follows: a total scale score (23 items), a physical health summary score (8 items) and a psychosocial health summary score (15 items). A 5-point response scale was used (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; and 4 = almost always a problem). The items were reverse-scored and linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). Higher scores were indicative of better HRQoL. The Swedish version of PedsQL has acceptable reliability and validity (70).
Hospital Anxiety and Depression Scale (HAD) (Study IV)
The Hospital Anxiety and Depression Scale (HAD) is a fourteen-item scale that generates ordinal data (71). Seven of the items pertain to anxiety, and seven, to depression. Each item is rated on a 4-point scale as follows: 0 = not at all, 1 = sometimes, 2 = often; and 3 = all the time, for maximum subscale score of 21 for both anxiety and depression. HAD yields clinically meaningful results as a psychological screening tool in clinical group comparisons and correlation studies and it addresses several aspects of disease and quality of life (72). Regarding the validation of the questionnaire, a score >7 in the two subscales distinguishes non cases from suspected cases. The questionnaire has adequate test-retest reliability and distinguishes between adolescents diagnosed with either depression or anxiety and adolescents without these diagnoses (73).

Physical activity (Study IV)
The adolescents wore an accelerometer (Actical™ Mini Mitter CO, Bend, OR, USA) over their right ankle for seven consecutive days and nights with instructions to remove the device only when bathing or showering. The accelerometer (dimensions: 2.8 x 2.7 x 1.0 centimetres; weight: 17 grams) measured and recorded time-stamped acceleration in all directions. The monitors collected data in 60-second intervals. The adolescents were blinded to the data while wearing the devices. Following the seven-day period, the monitors were collected, and the data were downloaded and archived. The raw accelerometer data files were visually inspected for compliance and data integrity using the manufacturer’s software (Actical V2.0, Mini Mitter Co., Inc.). Each accelerometer file had to satisfy the following criteria before it underwent further processing: the subject must have worn the monitor for at least four full days during the specified period, and a “full day of wearing” was defined as at least 10 hours of continuous monitoring from the first to the last bursts of activity data. The cut off points developed by Heil et al. (74) were used to calculate the time spent engaged in moderate to vigorous physical activity. For each respondent, the minutes of moderate to vigorous physical activity were summed for each day and averaged for valid days.
Statistical methods

The analysis used in studies I-IV are presented in table 4

Table 4. Data analysis used in studies I-IV

<table>
<thead>
<tr>
<th>Methods</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Descriptive analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median and range</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbers and frequencies</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Mean and standard deviation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Inferential analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson’s chi squared test</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fishers exact test</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Unpaired Student’s t-test</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Mann-Whitney U test</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theory for stratified samples</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Linear regression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logistic regression</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The analysis strategy was based on the type of data collected (categorical or continuous) and the distribution of data. Non–normally distributed variables and categorical data were analysed using non-parametric methods or transformed to normalized data. All statistical tests were two-sided and comparisons with a probability of error < 5% were considered significant. Data were analysed using the Statistical Package for Social Science (SPSS) software version 19 (SPSS Inc. Chicago, IL, USA).

Study I

The continuous variables were summarised as the means and standard deviations (SD). The categorical variables were summarised as numbers and percentages. For all categorical variables, a cross-tabulation vs. subject groups was performed, and the subject groups were compared using a Pearson’s chi-squared test. Continuous data were compared using unpaired t-tests. A logistic regression analysis (odds ratios (OR) and 95% confidence intervals (CI)) was performed using exercise-induced dyspnoea as the dependent variable and gender, ever-asthma, rhinitis and overweight and obesity used as independent variables.

Study II

Anthropometric data, lung function, asthma medication and exercise test results were summarised as the means, standard deviations (SD) and minimal and maximal for continuous variables, and as numbers and percentages for categorical variables. Age, BMI, and FEV₁ were compared between sub-
ject groups using unpaired Student’s t tests. For all of the categorical variables, a cross-tabulation vs. subject groups was performed and subject groups were compared using a Pearson’s chi-squared test/ Fisher’s exact test.

The EIB and E-ILO prevalence estimates were based on the assumption that the population strata with and without exercise-induced dyspnoea differed. Assuming that there was no selection bias, the dyspnoea stratum with exercise-induced dyspnoea was calculated from the rate of exercise-induced dyspnoea among responders times the population size, and the stratum without exercise-induced dyspnoea was assumed to represent the rest of the population. The adolescents who underwent the EIB- and the CLE tests were assumed to be random samples from the two strata. The prevalence estimate and the 95 % CI were calculated according to the theory for stratified samples (75).

**Study III**

Height, weight, lung function, asthma medication and exercise test results were summarised as the means and standard deviations (SD) for continuous variables and as numbers and percentages for categorical variables. The distribution of the levels of FeNO were skewed to the right and were therefore log-transformed and presented as geometrical means (95% CI). Age, body mass index (BMI), FVC, FEV1 recorded at baseline, and the level of FeNO was compared between subject groups using unpaired Student’s t tests. For all categorical variables, a cross-tabulation vs. subject groups was performed, and the groups were compared using a Pearson’s chi-squared test/ Fisher’s exact test. A logistic regression analysis (OR with 95% CI) was performed using EIB as the dependent variable and using the covariates: FEV1 (% pred), FeNO, use of ICS, gender, asthma and exercise-induced dyspnoea. Independent variables with a p-value <0.05 were entered (forced entry) into the multiple regression.

**Study IV**

The continuous variables were summarised as either the means and standard deviations (SD) or medians and interquartile ranges (IQR). The categorical variables were summarised as numbers and percentages. Age, BMI, FVC and FEV1, HRQoL, anxiety and depression scores and physical activity levels were compared between the groups using either unpaired Student’s t tests or Mann-Whitney U-test. For all categorical variables, a cross-tabulation vs. subject groups was performed, and the subject groups were compared using either a Pearson’s chi-squared test/ Fisher’s exact test. A univariate linear regression analysis (with 95% CI) was performed, with HRQoL (total and physical scores) and FEV1 serving as the dependent variables and EIB serving as the independent variable, both unadjusted and adjusted for the variable asthma and stratified for gender. Insignificant variables were removed
from the model to obtain the simplest model that provided the greatest explanatory power.
Results

Prevalence of exercise-induced dyspnoea (Study I)

Participant characteristics are presented in table 5.

The prevalence of exercise-induced dyspnoea was 14.3% (n=330). The prevalence of asthma was 14.6% and both exercise-induced dyspnoea and asthma were reported by 5.4% (n=128) of the adolescents (figure 2). In total 220 (66.7%) adolescents reporting exercise-induced dyspnoea had never been diagnosed by a physician as having asthma. Female adolescents reported exercise-induced dyspnoea to a greater extent compared to males both in the total population and the subgroup containing individuals with exercise-induced dyspnoea without asthma (figure 3).

Table 5. Characteristics for the total study population and adolescents with and without exercise-induced dyspnoea Results are presented as number, n (%).

<table>
<thead>
<tr>
<th></th>
<th>Total study population</th>
<th>Exercise-induced dyspnoea</th>
<th>No Exercise-induced dyspnoea</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=2309</td>
<td>n=330</td>
<td>n=1979</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise-induced dyspnoea</td>
<td>330 (14.3%)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>338 (14.6%)</td>
<td>128 (38.7%)</td>
<td>210 (10.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female/male (%)</td>
<td>49.2 / 50.8</td>
<td>58.2 / 41.8</td>
<td>47.7 / 52.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overweight and obesity</td>
<td>346 (15.0%)</td>
<td>58 (17.6%)</td>
<td>288 (15.0%)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

* Self-reported, having ever been diagnosed by a physician as having asthma, †Overweight and obesity defined as body mass index kg/m² (BMI) ≥25, age and sex specific cut off point for children.

P-value: Exercise-induced dyspnoea versus No exercise-induced dyspnoea.
Figure 2. Number, n (%) of adolescents with exercise-induced dyspnoea, exercise-induced dyspnoea and asthma and only asthma out of the total population n=2309.

Figure 3. Percentage of female and male adolescents reporting exercise-induced dyspnea in the total population (n=2309), no asthma group (n=1971) and asthma group (n=338).
Prevalence of EIB and E-ILO (Study II)

The estimated prevalence of EIB was 19.2% (95% CI 9.9; 28.4) in the population of 3,838 adolescents, 18.6% in females and 19.7% in males (p = 0.91) (figure 4). EIB was present in 42 adolescents (42.4%) in the exercise-induced dyspnoea group and in seven adolescents (14.9%) in the control group.

The estimated prevalence of E-ILO in the population was 5.7% (95% CI 0.01; 11.4) with no gender differences (p>0.99) (figure 4). E-ILO was present in nine (10.8%) adolescents in the exercise-induced dyspnoea group and two (4.8%) adolescents in the control group.

Four (4.8%) of the adolescents with exercise-induced dyspnoea had both EIB and E-ILO (figure 5).

Of the adolescents with exercise-induced dyspnoea, 49.4% had neither EIB nor E-ILO. Significantly more males than females had neither EIB nor E-ILO (64.7% vs. 38.8% p=0.026) (figure 6).

Figure 4. Prevalence (%) of EIB and E-ILO in the total population and in females and males. EIB, exercise-induced bronchoconstriction; E-ILO, exercise-induced laryngeal obstruction.
Figure 5. EIB and E-ILO in adolescents reporting exercise-induced dyspnoea, n %. EIB, exercise-induced bronchoconstriction; E-ILO, exercise-induced laryngeal obstruction.

Figure 6. EIB and E-ILO in males and females reporting exercise-induced dyspnoea, n %. EIB, exercise-induced bronchoconstriction; E-ILO, exercise-induced laryngeal obstruction.
Temporal aspects of decline in FEV$_1$ after EIB test (Study III)

The responses to the EIB test (a standardised exercise test using dry-air ventilation) in the group of adolescents with and without a positive EIB test are shown in figure 7. The 49 adolescents with a positive EIB test showed a mean percentage decline of 18.7% (± 7.9%) in FEV$_1$. In the non-EIB group (n=91), the mean percentage decline in FEV$_1$ was 4.1% (± 3.5%).

In the group with a positive EIB test 12 of the 49 adolescents (24%) showed the greatest decline in FEV$_1$ at 5 min (mean decline 18.4 ±8.2%), 14 adolescents (29%) showed it at 10 min (mean decline 18.4 ±8.6%), 12 adolescents (25%) showed it at 15 min (mean decline 19.4 ±10.3%) and 11 adolescents (22%) showed it at 30 min (mean fall 21.5 ±10.9%) after the exercise test (figure 8). Fifteen of the adolescents with the largest decline at 5 or 10 min (58%) and four of the adolescents with the largest decline at 15 min (25%) recovered within 30 min (i.e., to a<10% decline in FEV$_1$) (figure 8).

Figure 7. Post-challenge percentage change in FEV$_1$ from baseline (mean, SEM) until 30 min after challenge for adolescents with a positive EIB test (dotted line, n=49) and for adolescents with a negative EIB test (continuous line, n=91). EIB, exercise-induced bronchoconstriction.
Variables contributing to the presence of exercise-induced dyspnoea and EIB (Studies I and III)

Having had a diagnosis of asthma (OR 5.00, CI 3.77-6.62), female gender (OR 1.80, CI 1.40-2.33) and rhinitis (OR 1.73, CI 1.29-2.32) were independently associated with an increased risk of exercise-induced dyspnoea (study I).

A FeNO level >20 ppb (OR 4.18, CI 1.53-11.5), female gender (OR 3.14, CI 1.28-7.68) and exercise-induced dyspnoea (OR 2.92, CI 1.03 – 8.30) were independently associated with a positive EIB test (study III).

Symptoms in adolescents with and without exercise-induced dyspnoea (Study I)

Adolescents with exercise-induced dyspnoea (n=330) reported rhinitis, wheezing and day-time and nocturnal dyspnoea more often than the group without exercise-induced dyspnoea (table 6).
Table 6. Symptoms of adolescents with (n=330) and without exercise-induced dyspnoea (n=1769), numbers (%).

<table>
<thead>
<tr>
<th></th>
<th>Exercise-induced dyspnoea n=330</th>
<th>No Exercise-induced dyspnoea n=1769</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinitis</td>
<td>100 (30.3%)</td>
<td>299 (15.1%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current wheeze</td>
<td>158 (47.9%)</td>
<td>116 (5.9%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day time dyspnoea</td>
<td>42 (12.7%)</td>
<td>31 (1.6%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nocturnal dyspnoea</td>
<td>81 (24.5%)</td>
<td>79 (4.0%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Among adolescents without asthma, adolescents with exercise-induced dyspnoea reported more rhinitis, wheezing, day-time and nocturnal dyspnea and absence from school compared to those without exercise-induced dyspnoea (p<0.001).

**Self-reported exercise induced respiratory symptoms in adolescents with EIB, E-ILO or exercise-induced dyspnoea (Study II)**

There were no differences in self-reported symptoms between adolescents diagnosed with EIB, E-ILO or exercise-induced dyspnoea without a diagnosis (table 7).

Table 7. Self-reported exercise induced respiratory symptoms in the group with exercise-induced dyspnoea and positive EIB test (EIB) and the group with exercise-induced dyspnoea and E-ILO with or without EIB (E-ILO) and in the group with exercise-induced dyspnoea (without EIB or E-ILO)

<table>
<thead>
<tr>
<th></th>
<th>EIB n=33</th>
<th>E-ILO n=9</th>
<th>Exercise-induced dyspnoea n=41</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough, n (%)</td>
<td>17 (52)</td>
<td>3 (33)</td>
<td>21 (51)</td>
<td>0.57</td>
</tr>
<tr>
<td>Chest tightness, n (%)</td>
<td>15 (45)</td>
<td>4 (44)</td>
<td>18 (44)</td>
<td>0.99</td>
</tr>
<tr>
<td>Throat tightness, n (%)</td>
<td>12 (36)</td>
<td>5 (56)</td>
<td>20 (49)</td>
<td>0.41</td>
</tr>
<tr>
<td>Wheeze, n (%)</td>
<td>13 (39)</td>
<td>3 (33)</td>
<td>17 (41)</td>
<td>0.87</td>
</tr>
<tr>
<td>Hoarse voice, n (%)</td>
<td>11 (33)</td>
<td>1 (11)</td>
<td>14 (34)</td>
<td>0.37</td>
</tr>
<tr>
<td>Choking sensation, n (%)</td>
<td>6 (18)</td>
<td>3 (33)</td>
<td>14 (34)</td>
<td>0.26</td>
</tr>
<tr>
<td>Inspiratory stridor, n (%)</td>
<td>9 (27)</td>
<td>1 (11)</td>
<td>11 (27)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

EIB, exercise-induced bronchoconstriction; E-ILO, exercise-induced laryngeal obstruction. p-value = cross tabulation between all three groups.
HRQoL, anxiety and depression, and symptoms in adolescents with and without EIB (Studies II-IV)

In the total group (n=140), adolescents with EIB (n=49) exhibited lower HRQoL and higher anxiety scores than those without EIB (table 8). Exercise-induced dyspnoea, asthma, asthma medication usage, and sleep disturbances were more common among the adolescents with EIB and they had higher levels of FeNO and lower values of FEV₁ % predicted at baseline than those without EIB (table 8).

Table 8. Characteristics of adolescents with and without a positive EIB test. Data are presented as n (%) or mean ±SD unless otherwise indicated.

<table>
<thead>
<tr>
<th></th>
<th>EIB n=49</th>
<th>No EIB n=91</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (min,max)</td>
<td>14.3 (13,15)</td>
<td>14.2 (13,15)</td>
<td>0.31</td>
</tr>
<tr>
<td>Female</td>
<td>36 (73)</td>
<td>48 (53)</td>
<td>0.017</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.3 ±2.8</td>
<td>20.8 ±2.9</td>
<td>0.30</td>
</tr>
<tr>
<td>Overweight and obesity</td>
<td>6 (12)</td>
<td>9 (10)</td>
<td>0.67</td>
</tr>
<tr>
<td>Exercise-induced dyspnoea</td>
<td>42 (86)</td>
<td>52 (57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asthma</td>
<td>22 (45)</td>
<td>18 (20)</td>
<td>0.002</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>17 (35)</td>
<td>30 (33)</td>
<td>0.84</td>
</tr>
<tr>
<td>FeNO (ppb) geometric mean (95%CI)</td>
<td>18.3 (14.8–22.7)</td>
<td>13.1 (11.6–14.8)</td>
<td>0.004</td>
</tr>
<tr>
<td>FeNO &gt;20 ppb</td>
<td>19 (39)</td>
<td>14 (16)</td>
<td>0.002</td>
</tr>
<tr>
<td>FVC% predicted†</td>
<td>93 ±11</td>
<td>95 ±11</td>
<td>0.31</td>
</tr>
<tr>
<td>FEV₁% predicted†</td>
<td>90 ±9</td>
<td>94 ±11</td>
<td>0.049</td>
</tr>
<tr>
<td>IgE sensitisation</td>
<td>21 (43)</td>
<td>41 (45)</td>
<td>0.80</td>
</tr>
<tr>
<td>Inhaled corticoid steroids</td>
<td>14 (28.6)</td>
<td>11 (12.1)</td>
<td>0.015</td>
</tr>
<tr>
<td>Short acting beta-2-agonist</td>
<td>22 (44.9)</td>
<td>22 (24.2)</td>
<td>0.012</td>
</tr>
<tr>
<td>Disturbed sleep</td>
<td>9 (18.4)</td>
<td>1 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety, median (IQR)</td>
<td>6 (5)</td>
<td>4 (4)</td>
<td>0.007</td>
</tr>
<tr>
<td>Depression, median (IQR)</td>
<td>2 (4)</td>
<td>2 (3)</td>
<td>0.78</td>
</tr>
<tr>
<td>HRQoL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>80.6 ±13.8</td>
<td>85.8 ±11.8</td>
<td>0.029</td>
</tr>
<tr>
<td>Physical score</td>
<td>81.3 ±13.3</td>
<td>87.0 ±12.4</td>
<td>0.011</td>
</tr>
<tr>
<td>Psychosocial score</td>
<td>80.7 ±15.5</td>
<td>85.1 ±12.5</td>
<td>0.074</td>
</tr>
</tbody>
</table>

EIB; exercise-induced bronchoconstriction, BMI; body mass index (kg/m²), FeNO; fraction of nitric oxide (NO) in exhaled air, HAD; Hospital anxiety and depression scale, HRQoL; Health related quality of life

Self-reported, having ever been diagnosed by a physician as having asthma

†Forced vital capacity (FVC) and FEV₁ presented as percentage of predicted recorded at baseline before EIB test.

Independent of having EIB or not, in the total group, female adolescents had lower HRQoL than males (total scores 81.3 vs. 88.1 p=0.002, physical scores 81.8 vs. 89.9 p<0.001 and psychosocial scores (81.1 vs.87.2
In addition, female adolescents also had higher anxiety, but did not have higher depression scores than males (5.0 vs 3.0, \( p<0.001 \)).

Females with EIB (n=36) had lower HRQoL and higher anxiety scores than females without EIB (n=48) (table 9 and figure 9). Females with EIB also exhibited lower baseline FEV\(_1\) values, and a larger proportion of these individuals reported exercise-induced dyspnoea, asthma, sleep disturbances, and use of asthma medications than females without EIB (table 8). Among the males, there were no differences in any of the investigated variables between the adolescents with and without EIB (table 9 and figure 9).

Table 9. Characteristics of females with and without EIB and males with and without EIB. Data are presented as mean ±SD or n (%) unless otherwise indicated.

<table>
<thead>
<tr>
<th></th>
<th>Female EIB N=36</th>
<th>Female No EIB N=48</th>
<th>p-value</th>
<th>Male EIB N=13</th>
<th>Male No EIB N=43</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI</strong></td>
<td>21.7 ±3.0</td>
<td>20.5 ±2.9</td>
<td>0.086</td>
<td>20.5 ±1.7</td>
<td>21 ±3.1</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Overweight and obesity</strong></td>
<td>6 (16.7)</td>
<td>4 (8.3)</td>
<td>0.31</td>
<td>0</td>
<td>5 (11.6)</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Exercise-induced dyspnoea</strong></td>
<td>33 (91.7)</td>
<td>26 (54.2)</td>
<td>&lt;0.001</td>
<td>9 (69.2)</td>
<td>26 (60.5)</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td>17 (47.2)</td>
<td>7 (14.6)</td>
<td>0.001</td>
<td>5 (38.5)</td>
<td>11 (28.9)</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Rhinitis</strong></td>
<td>11 (30.6)</td>
<td>15 (31.3)</td>
<td>0.95</td>
<td>6 (46.2)</td>
<td>15 (34.9)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>FVC% predicted</strong></td>
<td>91.1 ±10.6</td>
<td>94.0 ±11.7</td>
<td>0.22</td>
<td>98.4 ±10.5</td>
<td>96.2 ±11.7</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>FEV(_1)% predicted</strong></td>
<td>88.8 ±8.4</td>
<td>94.4 ±10.6</td>
<td>0.012</td>
<td>94.5 ±10.9</td>
<td>93.6 ±10.5</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Inhaled corticoid steroids</strong></td>
<td>11 (30.1)</td>
<td>5 (10.4)</td>
<td>0.020</td>
<td>3 (23.1)</td>
<td>6 (14.0)</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Short acting beta-2-agonist</strong></td>
<td>19 (52.8)</td>
<td>11 (22.9)</td>
<td>0.005</td>
<td>4 (30.8)</td>
<td>12 (27.9)</td>
<td>0.84</td>
</tr>
<tr>
<td><strong>Disturbed sleep</strong></td>
<td>8 (22.2)</td>
<td>0</td>
<td>0.001</td>
<td>1 (7.7)</td>
<td>1 (2.3)</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>HAD Anxiety, median (IQR)</strong></td>
<td>7 (4)</td>
<td>4 (6)</td>
<td>0.031</td>
<td>3 (4)</td>
<td>3 (4)</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>HAD Depression, median (IQR)</strong></td>
<td>2 (4)</td>
<td>2 (3)</td>
<td>0.74</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>HRQoL Total score</strong></td>
<td>77.5 (12.6)</td>
<td>84.1 (13.4)</td>
<td>0.034</td>
<td>90 (5.8)</td>
<td>87.6 (9.6)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>HRQoL Physical score</strong></td>
<td>77.2 (14.4)</td>
<td>85.2 (14.2)</td>
<td>0.009</td>
<td>92.6 (7.1)</td>
<td>89 (9.8)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>HRQoL Psychosocial score</strong></td>
<td>77.9 (16.8)</td>
<td>83.5 (13.8)</td>
<td>0.09</td>
<td>88.7 (6.5)</td>
<td>86.8 (10.8)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

EIB: exercise-induced bronchoconstriction, BMI: body mass index (kg/m\(^2\)), HAD: Hospital anxiety and depression scale, HRQoL: health related quality of life

* Self-reported, having ever been diagnosed by a physician as having asthma

†Forced vital capacity (FVC) and FEV\(_1\) presented as percentage of predicted recorded at baseline before EIB test.
In females, EIB was significantly associated with both a lower total score and a lower physical function score in HRQoL in the univariate analysis. Following adjustment for asthma, this correlation was no longer significant. There was a significant association between EIB and low baseline FEV₁ values in females in both the univariate and the multivariate analyses. In males, there were no associations between the variables (table 10).

Table 10. Association between the dependent variables HRQoL and FEV₁% predicted and the independent variable EIB, unadjusted and adjusted for the variable asthma, stratified for gender.

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Female Unadjusted</th>
<th>Female Adjusted for asthma</th>
<th>Male Unadjusted</th>
<th>Male Adjusted for asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B (95% CI)</td>
<td>B (95% CI)</td>
<td>B (95% CI)</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td>Total score</td>
<td>-6.60 (-12.7 to -5.3)</td>
<td>-3.79 (-10.1 to 2.5)</td>
<td>2.50 (-3.2 to 8.1)</td>
<td>2.88 (-2.8 to 8.6)</td>
</tr>
<tr>
<td>Physical score</td>
<td>-8.07 (-14.0 to -2.1)</td>
<td>-5.6 (-11.8 to 0.62)</td>
<td>3.51 (-2.4 to 9.4)</td>
<td>3.74 (-2.2 to 9.7)</td>
</tr>
<tr>
<td>FEV₁% predicted</td>
<td>-5.57 (-9.8 to -1.3)</td>
<td>-4.77 (-9.4 to -0.15)</td>
<td>1.10 (-5.6 to 7.8)</td>
<td>2.20 (-4.2 to 8.6)</td>
</tr>
</tbody>
</table>

HRQoL; Health related quality of life, FEV₁; FEV₁ presented as percentage of predicted recorded at baseline before EIB test, EIB; Exercise-induced bronchoconstriction. B; regression coefficient, CI; confidence interval. asthma; Self-reported, having ever been diagnosed by a physician as having asthma
Physical activity (Studies I and IV)

Self-reported physical activity (study I)
On average, the adolescents were physically active 4.1 days per week for a total of at least 60 minutes per day. Only 12% of the total population was physically active ≥ 60 minutes per day seven days per week as is recommended in international guidelines. The group of adolescents reporting exercise-induced dyspnoea were physically active on average 4.3 days per week compared to 4.1 days in the group without exercise-induced dyspnoea \((p=0.045)\). Regarding the proportion of adolescents being physically active according to guidelines, no difference was found, between either the groups with and without exercise-induced dyspnoea or between the groups with and without ever-asthma.

Objectively measured physical activity (Study IV)
In the whole group \((n=130)\), the average minutes per day with MVPA was 54 minutes and males were more physically active than females (59.6 vs. 48.5 minutes, \(p=0.017\)). No differences in minutes per day in moderate to vigorous physical activity were found between adolescents with and without EIB; nor were there any differences within each gender (figure 10).

![Figure 10. Comparison of average minutes of moderate to vigorous physical activity in the total group and female and male adolescents with and without EIB. EIB: exercise-induced bronchoconstriction](image)

\(\text{Figure 10. Comparison of average minutes of moderate to vigorous physical activity in the total group and female and male adolescents with and without EIB. EIB: exercise-induced bronchoconstriction}\)
Discussion

Exercise-induced dyspnoea was reported by 14% of the adolescents. After standardised exercise testing of a random subsample with and without exercise-induced dyspnoea, the estimated prevalence of EIB and E-ILO in the total population is 19.2% and 5.7%, respectively.

When testing for EIB using standardised exercise challenge test with inhalation of dry air, temporal variation was observed in the greatest fall in FEV₁ declines after exercise. Half of the adolescents with a positive EIB test showed the greatest decline 5 to 10 minutes after exercise cessation while the remaining half showed the greatest decline at 15 to 30 minutes after exercise cessation.

Asthma, female gender and rhinitis were independently associated with self-reported exercise-induced dyspnoea. An increased baseline level of FeNO, female gender, and exercise-induced dyspnoea were independently associated with a positive EIB test.

Female adolescents with EIB had lower HRQoL and lower baseline lung function compared to females without EIB. These differences were not observed in male adolescents. Neither having exercise-induced dyspnoea nor having EIB appeared to affect the level daily physical activity among the studied adolescents.

Prevalence

*Exercise-induced dyspnoea*

Fourteen percent of the adolescents reported exercise-induced dyspnoea. Previous prospective studies investigating the prevalence of self-reported respiratory symptoms in conjunction with exercise have mainly been focused on asthma. The prevalence of exercise related wheezing has been reported to be 19% in the general population of adolescents (1, 28). We used the question “Have you had an attack of shortness of breath that happened after strenuous activity at any time during the last 12 months?” to investigate exercise-induced dyspnoea; this question has previously been used in population based studies and it has been proven to be sensitive for the diagnosis of asthma (59, 76). Although it is sensitive for asthma the question was used with the intention of capturing a broader range of exercise-induced breathing
problems. We found that 67% of the adolescents who reported exercise-induced dyspnoea did not have a diagnosis of asthma. In a Spanish study of exercise wheezing, 40% of the adolescents who reported wheezing had never been diagnosed with asthma (28). This difference might indicate that the question to investigate the prevalence of exercise-induced dyspnoea, as it was used in our study, might have captured a broader range of respiratory problems than only exercise-related wheezing, which might have increased the prevalence of reported respiratory problems in conjunction with exercise.

**EIB**

The prevalence of EIB was investigated using standardised exercise tests. The estimated population prevalence was 19.2%. Almost 40% of the adolescents with and 15% of the adolescents without self-reported exercise-induced dyspnoea were diagnosed with EIB. More than half of these adolescents had never been diagnosed with asthma. These results confirm previous studies reporting that EIB is underdiagnosed (26, 77).

On the other hand, overdiagnosis of EIB has been reported, when the diagnosis is based on symptoms alone. Apart from wheezing, reported symptoms of EIB include shortness of breath, chest tightness and coughing during or immediately after exercise and more subtle symptoms such as feeling out of shape and feeling unable to keep up with peers (78). There is however evidence showing that the diagnosis of EIB should not be made on the basis of history and self-reported symptoms alone (9). When in our study, in which self-reported respiratory symptoms were compared, there were no differences between adolescents with EIB, E-ILO or exercise-induced dyspnoea without a diagnosis. These results confirm that neither the diagnosis of EIB nor E-ILO should be made on the basis of symptoms alone.

**E-ILO**

In our study the estimated population prevalence of E-ILO (5.7%) was lower than the prevalence (7.6%) in the only other prospective population based study that has been published (12). These two studies are however, not truly comparable because the mean age of the adolescents differed (14.2 vs. 18.6 years old) and in the latter study only 98 of the 556 invited adolescents underwent the CLE test to diagnose E-ILO. In our study 9% of the adolescents with and 5% of the adolescents without exercise-induced dyspnoea were diagnosed with E-ILO.

We found no difference in prevalence between genders. In contrast, E-ILO has been reported to be more common among females than males (12, 79, 80). A possible reason for this finding could be the age of the population under study. One could speculate that in our research study a large proportion of the male adolescents had not yet gone through puberty. They may therefore have like females, a narrower larynx. In post-puberty at the age of 16-17 years, the male larynx has reaches its adult size (81) which has in-
creased diameter and less resistance and is therefore theoretically less prone to collapse.

In our study, 5% of the adolescents were diagnosed with both EIB and E-ILO confirming the results of previous case reports (45).

Despite the two standardised exercise tests used in our research study, in approximately half of the adolescents with exercise-induced dyspnoea neither EIB nor E-ILO could be demonstrated. The reason that these adolescents experience dyspnoea when exercising is unknown and not within the scope of this thesis. However, in previous retrospective studies of children who have exercise-induced dyspnoea, suspected by their primary care physician to have EIB and who had been treated without success for such, a majority did not actually have EIB. Instead, they were found to have restrictive abnormalities, VCD, exercise-induced hyperventilation, and for the most part, normal physiological limitations such as low cardiovascular conditioning (5, 6, 82, 83).

Exercise test using dry air ventilation

To diagnose EIB we used a standardised laboratory exercise challenge on a treadmill, during which relative humidity was controlled by letting the participant inspire dry air during the challenge. The most important determinants of EIB severity have been reported to be the water content of the inspired air and the level of ventilation achieved and sustained during exercise. The dryer the inspired air and the higher the ventilation during 6-8 minutes of exercise, the greater the likelihood of a positive response to exercise testing in a susceptible person (9, 14, 84-87). Ideally exercise ventilation should be measured and it should be above 60% of predicted maximum (i.e., greater than 21 times FEV₁). We chose to measure heart rate as a surrogate of ventilation. Guidelines recommend a target heart rate of 80 to 90% of the predicted maximum (9, 14, 27). Cardiac frequency was increased to 90% of the predicted maximum within the first 1.5 min, and this level was maintained throughout the 6-minute test by adjusting the treadmill speed and slope. By ensuring a relatively high workload and by letting the adolescents inspire dry air during the challenge the sensitivity of the EIB test might theoretically have been increased. This has been reported in other studies (32, 86).

In our studies, in accordance with international guidelines, a decrease ≥10% in FEV₁ as diagnostic criteria for EIB was used; this is a post exercise decrease that represents two standard deviations lower than the mean in healthy subjects (88, 89). It should be noted that using higher values for the percent fall in FEV₁ has been recommended to increase the specificity of the test (90, 91).
Temporal variation
Fifty percent of the adolescents with a positive EIB test showed a maximum post-exercise decline in FEV₁ at 5 or 10 minutes, while the other half showed a maximum decline at 15 or 30 min after exercise cessation. Post-exercise airway obstruction is reported to typically peak within 10 min (92, 93). In a study of patients with asthma (3-18 years old) the maximum post-exercise declines were found to be age-dependent in that the older the child the later the maximum post-exercise decline. However, none of the children reached a maximum post-exercise decline later than 12 min after exercise cessation (94). In contrast, in our research, some adolescents experienced a more prolonged (and even aggravated) obstruction after cessation of the exercise challenge. It would have been interesting to have obtained lung function measurements beyond 30 minutes. Breakthrough EIB (i.e., bronchoconstriction during exercise) has been studied in children and adolescents with asthma in whom it is found to be accompanied by a more severe decrease in lung function and a slower recovery from EIB, indicating uncontrolled asthma (95). Temporal differences in bronchial obstruction may indicate differences in underlying biological mechanisms. However, we found no differences in inflammatory variables between the groups with an earlier or later maximum post-exercise decline.

The group with the greatest decline in FEV₁ at 5 or 10 min was characterised by a larger proportion of females and a lower percentage of predicted baseline FVC and FEV₁ than the group with the greatest decline at 15 or 30 min. The association between gender and the time point of the greatest decline in FEV₁ after exercise has not previously been studied. Therefore, the current findings should be replicated and investigated further. The magnitude of the FEV₁ decline was not associated with the time point of the decline or baseline lung function values, which is consistent with previous findings (96).

Half of the subjects with the greatest post-exercise decline at 5 or 10 min and 75% of the subjects with the greatest post exercise decline at 15 min did not recover to baseline within 30 min. These data indicate that lung function should be measured for at least 30 min or perhaps even longer after exercise cessation if the aim is to investigate the greatest post-exercise decline in lung function and/or time to recovery.

HRQoL and anxiety
Adolescents with EIB reported lower HRQoL scores than adolescents without EIB and these results confirm those of previous studies (2, 49). In the present study a low HRQoL was associated with a female gender. In the general population female adolescents have been found to have lower
HRQoL according to both national and international studies (47, 97, 98). When within-gender differences were analysed in our research study, female adolescents with EIB were found to have lower total and physical HRQoL scores and higher levels of anxiety compared to females without EIB. These differences were not found in males. The relationship between EIB and HRQoL in females can be partially explained by the higher prevalence of asthma in female subjects with EIB. This result is supported by others studies that have found that female gender is an independent determinant of lower HRQoL in individuals with asthma (99). When comparing the summary scores from the PedsQL-instrument to reference values (100, 101) our female adolescents with EIB in study IV exhibited scores resembling those of adolescents with an asthma diagnosis. In contrast, the males with EIB exhibited scores in line with or even above those of healthy adolescents. Understanding gender-related differences in HRQoL in relation to EIB and asthma might be important when tailoring a management plan for each individual patient. Interventions that target asthma in females with EIB should have a positive effect on HRQoL and anxiety.

Physical levels of activity

We used both subjective and objective measures to assess daily level of physical activity. In study I, in which a questionnaire was used, no differences were found in physical activity between adolescents with or without exercise-induced dyspnoea. In study IV, using accelerometers as objective measures of physical activity, the same average amount of minutes per day with moderate- to vigorous physical activity was found in adolescents with and without EIB. These results are consistent with previous studies of children with newly diagnosed asthma and children exhibiting symptoms of asthma (102, 103). In contrast, children 10-12-years-old who tested positive for EIB, reported spending fewer minutes per day with moderate- to vigorous physical activity than controls (38). Children and adolescents with a diagnosis of asthma have been found in some studies to be as physically active as their healthy peers (104, 105) while others studies have reported lower levels of physical activity (106, 107). It has been argued that the level of physical activity in children and adolescents with asthma may appear artificially high because active children and adolescents are more likely to be diagnosed with asthma and EIB (108). This raises the question of how to measure physical activity levels. One could speculate that among subjects with EIB that self-reported levels of physical activity may differ from objectively measured levels. Therefore objective measures of levels of physical activity should be used.

It is however important to remember that measurements of the level of physical activity do not say anything about the physical capacity. Although
found to have the same level of physical activity the adolescents with EIB in this research might in fact not have the same capacity as adolescents without EIB. In fact, in a Swedish study children with newly diagnosed, untreated asthma were found to be less fit despite the fact that they had the same level of daily physical activity as healthy controls (103). In future studies on exercise-induced dyspnoea and EIB, there is a need to investigate both physical activity and capacity.

Methodological discussion

The response rate (60.2%) of those who responded to our initial questionnaire is satisfactory. There were no difference in age, gender or postal area codes between responders and non-responders. There is a possibility of bias caused by those experiencing exercise-induced breathing problems and/or asthma being more prone to answer the questionnaire, which would affect results relating to the prevalence.

The questionnaire was not scientifically tested for reliability or validity but several of the questions included have previously been used in large population based studies. Before distributing the questionnaire face-validity of the questionnaire was tested on a convenience sample of 20 adolescents with the same age as the population under study. All of these individuals agreed that the questionnaire was easy to understand and answer. Recall bias was reduced by asking only for symptoms that occurred during the last 12 months and by asking the guardian and the adolescent to fill out the questionnaire together.

There is a potential bias in the sampling procedure used in study II. The aim was to include, by randomised order, approximately 100 adolescents (one-third of all adolescents with exercise-induced dyspnoea) with and 50 adolescents without exercise-induced dyspnoea as controls. Of the 199 contacted adolescents who had exercise-induced dyspnoea 96 adolescents declined participation, while 76 of the 123 adolescents without exercise-induced dyspnoea declined participation. There were no differences in age, BMI, wheezing, rhinitis, day-time or night-time dyspnoea or absence from school between participating adolescents and those declining participation. In the group with exercise-induced dyspnoea, a larger proportion of adolescents reported having been diagnosed with asthma than was reported by those declining participation. This could possibly have influenced the prevalence numbers. In our study, asthma was defined as a positive answer to the question “Have you ever been diagnosed by a physician as having asthma”. A purposefully broad notion was used to increase the sensitivity of the question. It is not impossible that subjects with exercise-induced dyspnoea that was found to be related to E-ILO in our study would at some time in their life have been diagnosed with asthma.
A strength of this study is the use of standardised exercise tests to diagnose EIB and E-ILO. However, one can consider threats to the construct validity of the EIB test. First, the adolescents were only tested once. In the general population one cannot rule out a variable test response because airway hyperactivity might vary over time. However, the reproducibility of a standardised EIB test has been investigated in subjects without a definite diagnosis of asthma and a majority of the tested subjects had the same outcome on both test-occasions (109). Second, appropriate timing of the withdrawal of inhaled corticosteroids may not have been done according to guidelines. This may possibly have resulted in false negative test results because approximately one-tenth of the adolescents without EIB reported use of ICS during the last three months. Third, the level of ventilation reached and sustained during the exercise challenge is a determinant of the fall in FEV\textsubscript{1} (93). There are known technical difficulties in measuring ventilation while simultaneously administrating dry air during exercise. Therefore a heart rate of 90\% of the estimated maximal heart rate was used as a surrogate measure of ventilation (Study III). This has been previously recommended as a surrogate for > 40\% of maximum voluntary ventilation (14, 93). It has been suggested that increasing the heart rate of 95\% of predicted maximum during the challenge might increase the sensitivity of the test even further (32).

It is likely that the use of the CLE test to diagnose E-ILO increased the accuracy of diagnosis. No other method (including spirometry) has been proven to reliably predict E-ILO. However, although descriptions of laryngoscopic findings were emphasized in a recent review of inducible laryngeal obstruction (18) there is at this point no agreement regarding how to differentiate between a normal and an abnormal CLE test.

Attempts to achieve internal validity were made in the present studies. To reduce the experimenter expectancy effect, the investigators performing the exercise tests were blinded to whether or not the adolescents had reported exercise-induced dyspnoea or and to the result of the EIB test. The same experimenter conducted, according to a standardised protocol, all EIB tests, and another experimenter conducted all of the CLE tests, thus decreasing measurement bias and decreasing threats to instrumentation bias.

**External validity**

The results of the studies included in this thesis are valid for adolescents 12-15 years old with (and without) self-reported exercise-induced breathing problems, (primarily without a diagnosis) who were willing to participate in a medical evaluation using standardised exercise tests. However, because the response rate of the initial questionnaire was 60\% and since there were a large number of adolescents declining participation in the exercise tests the generalization of the results might be restricted.
Conclusions

The prevalence of exercise-induced dyspnoea is 14% in a general adolescent population and more females than males are affected.

The estimated prevalence of EIB is 19.1% and of E-ILO 5.7% in a general adolescent population. E-ILO is not uncommon, thus it is an important differential diagnosis to EIB. EIB and E-ILO are not mutually exclusive but can co-exist. There are no gender differences in the estimated prevalence of EIB and E-ILO in the adolescent population.

When assessing general adolescents for EIB with exercise test using dry air, there is a temporal variation in the greatest FEV₁ decline after exercise. Therefore, lung function should be measured for at least 30 min after the exercise.

Increased levels of FeNO, female gender and self-reported exercise-induced dyspnoea are variables that are associated with a positive EIB test in the adolescent population.

There are no differences in self-reported exercise induced respiratory symptoms between adolescents with EIB, E-ILO or exercise-induced dyspnoea without a diagnosis.

Female adolescents with EIB have lower HRQoL scores than females without EIB. These differences are not observed in males.

Neither self-reported exercise-induced dyspnoea nor EIB seems to affect the level of daily physical activity among adolescents.

Clinical implications

Clinicians should be aware that exercise-induced dyspnoea is common among adolescents. EIB is the most common but not the only cause of experiencing respiratory problems in conjunction with exercise. E-ILO is not uncommon and is therefore an important differential diagnosis to EIB. Standardised exercise tests are needed to confirm a diagnosis of EIB and E-ILO because their symptoms are non-specific. A correct diagnosis means that correct medical treatment can be offered, but it is equally important to cease unnecessary treatment.

In adolescents with EIB special attention should be given to females because they report impaired HRQoL.
Future research

Because half of the investigated adolescents with exercise-induced dyspnoea did not have a positive EIB or E-ILO test, further studies are needed to explain the underlying reason for this phenomenon. Therefore, in future studies it would not only be of interest to include other medical examinations but also to follow subjects with undiagnosed exercise-induced dyspnoea to determine whether they develop asthma or other conditions over time.

At this point there is evidence showing that neither a diagnosis of EIB nor a diagnosis of E-ILO should be based on history and self-reported symptoms alone. Still exercise challenge tests are not always readily available (especially in a primary care setting) and they can be costly and time consuming. Therefore, in the future there is a need to develop a valid EIB and E-ILO diagnostic/screening questionnaire.

In international guidelines standardised exercise challenge tests with the use of inhalation of dry air are recommended as the diagnostic tool for EIB. There is a need for future studies using this method to better understand the different response pattern observed in lung function in these tests.
Det är inte ovanligt med ansträngningsutlösta andningsbesvär bland ungdomar. Trots detta är orsakerna till besvären inte kartlagda. Två tänkbara orsaker till dessa respiratoriska besvär i samband med fysisk aktivitet är ansträngningsutlöst bronkobstruktion (exercise-induced bronchoconstriction; EIB) och ansträngningsutlöst obstruktion i struphuvudet (exercise-induced laryngeal obstruction; E-ILO).

EIB definieras som en övergående sammandragning av de nedre luftvägarna utlöst av fysisk ansträngning (i dagligt tal ansträngningsutlöst astma). E-ILO omfattar en grupp av tillstånd som involverar stämband och strukturer i närområdet av stämbanden i struphuvudet där luftvägsobstruktion uppstår i samband med fysisk ansträngning och som oftast är snabbt övergående efter vila. Internationella riktlinjer rekommenderar standardiserat ansträngnings- test med samtidig inhalation av torrluft för att diagnosticera EIB. E-ILO diagnosticeras med hjälp av videolaryngoskopi (filmpåtagande av struphuvudet) under ansträngning. Trots sina olika underliggande orsaker kan symptommen vara relativt lika vid EIB och E-ILO. Få tidigare tvärsnitts-studier har med hjälp av standardiserade ansträngnings- test undersökt hur vanligt det är med EIB och E-ILO bland ungdomar i en normalpopulation.

I det dagliga arbetet med barn och ungdomar med ansträngningsutlösta andningsbesvär är det av vikt för kliniker att veta hur vanliga dessa tillstånd är och hur tillstånden påverkar dagligt liv hos ungdomar.

Det övergripande syftet med denna avhandling var att undersöka hur vanligt det är med ansträngningsutlösta andningsbesvär, förekomsten av EIB och E-ILO samt hur EIB påverkar dagligt liv bland ungdomar i en normalpopulation.


I delstudie II-IV slumpades 150 ungdomar fram som besvarat enkäten (103 ungdomar med och 47 ungdomar utan ansträngningsutlösta andningsbesvär). De deltog i tre besök på sjukhus. Vid besök 1 intervjuades ungdo-
marna om bland annat astma och medicinering och fyllde i frågeformulär om livskvalitet och oro och ångest. Dessutom mättades utandad kväveoxid (FeNO, ett mätt på inflammation i luftvägarna). Vid besök 2 genomfördes ett ansträngningstest på löpband med samtidig inhalation av torrluft, i syfte att diagnosticerar EIB. Lungfunktion (FEV\textsubscript{1}) mättes före och upp till 30 minuter efter ansträngning på löpband. Ett positivt test definierades som ett fall i FEV\textsubscript{1} >10%. Efter besöket registrerades ungdomarnas fysiska aktivitet objektivt under sju dagar med hjälp av aktivitetsmätare placerad runt fotleden.

Vid besök tre genomfördes ansträngningstest på löpband under samtidig filmning av struphuvudet med laryngoskop i syfte att diagnosticerar E-ILO.

I hela populationen var den beräknade förekomstena av EIB 19,2% och av E-ILO 5,7%. Det var ingen skillnad i förekomst av EIB eller E-ILO mellan könen. Bland de ungdomar med ansträngningsutlösta andningsbesvär som genomförde besöken på sjukhus hade 40% EIB, 6% E-ILO och 5% hade både EIB och E-ILO. Vi fann ingen skillnad vad gäller typen av självrapporterade symtom mellan ungdomar med EIB respektive E-ILO.

Ökade nivåer av FeNO, kvinnligt kön och självrapporterade ansträngningsutlösta andningsbesvär var alla faktorer som predicerade ett positivt EIB test.

Vad gäller påverkan på dagligt liv fann vi att ungdomar med EIB skattade lägre livskvalitet och rapporterade mer oro jämfört med ungdomar utan EIB. Det var framförallt flickor med EIB som var påverkade, då denna grupp skattade lägre livskvalitet och rapporterade mer oro jämfört med flickor utan EIB. I motsats till flickor var det bland pojkar ingen skillnad mellan de med och utan EIB. Det var ingen skillnad i daglig fysisk aktivitet mellan ungdomar med och utan EIB.


Särskild uppmärksamhet bör riktas mot flickor med EIB eftersom de rapporterar mer negativ påverkan på dagligt liv. Dock verkar inte EIB påverka graden av daglig fysisk aktivitet.
Acknowledgements

Jag vill framföra ett stort och varmt tack till alla personer som varit viktiga för mig under min forskarutbildning och i arbetet med denna avhandling. Ett stort tack till alla ungdomar och föräldrar som deltagit i studierna.

Framförallt vill jag tacka

Margareta Emtner, min huvudhandledare, för att du stimulerade mig att börja, för att du på ett tydligt, tillgängligt, entusiastiskt och alltid lagom stödjande sätt handlett mig. Margareta, du inspirerar och motiverar!

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Min familj Mamma Kerstin och pappa Mats, tack för all kärlek och allt stöd (och för att ni var med och klistrade alla dessa lappar och slickade alla dessa kuvert).

Mina bröder Martin och Jakob med familjer, tack för stödning och uppmuntran.

Mina barn Elias, Alvar, Tyra och Edvin, tack för att ni hjälpt till vid datainsamling och varit ”försökskaniner” på rullband och vid lungfunktionsmätning men framförallt för att Ni är det viktigaste och bästa i mitt liv!

Min fru Sophie, tack för stöd, delad vardagslogistik, för din klarsynthet men framförallt för att Du är det bästa och viktigaste i mitt liv!!


Personlig kod i studien _______

Skriv in din personliga kod som du hittar i högra hörnet på följebrevet du fick med posten

Ålder ________år

Är du:
☐ Flicka ☐ Pojke

1. Har du haft pip- eller har det väst i bröstet vid något tillfälle under de senaste 12 månaderna?

☐ Ja ☐ Nej ➔ Fråga 2

Om Ja, på föregående fråga

1b. Hur många episoder med pipande eller väsande andning har du haft under de senaste 12 månaderna?

☐ 1-3 gånger ☐ 4-12 gånger ☐ Fler än 12 gånger

2. Har du vaknat med en trånghetskänsla i bröstet vid något tillfälle under de senaste 12 månaderna?

☐ Ja ☐ Nej

3. Har du någon gång under de senaste 12 månaderna haft något anfall av andnöd som inträffat på dagtid under vila?

☐ Ja ☐ Nej

4. Har du någon gång under de senaste 12 månaderna haft någon andnödsattack som kommit efter ansträngning?

☐ Ja ☐ Nej

5. Har du vaknat av andnödsattack vid något tillfälle under de senaste 12 månaderna?

☐ Ja ☐ Nej

6. Har du haft andningsbesvär eller andra besvär från luftvägarna under de senaste 12 månaderna?

☐ Ja ☐ Nej ➔ Fråga 8

Om Ja, på föregående fråga gå till fråga 7
7. Vilka orsaker till dina andnings-/luftvägssbesvär har du märkt av?

Kryssa ett alternativ för varje orsak.

<table>
<thead>
<tr>
<th>Orsak</th>
<th>Aldrig</th>
<th>Ibland</th>
<th>Alltid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Övre luftvägsinfektion/förkylning</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Ansträngning</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Kall luft</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Väderomslag</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Damm</td>
<td>□</td>
<td>□</td>
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<tr>
<td>Mögeldoft</td>
<td>□</td>
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<tr>
<td>Cigarettrök</td>
<td>□</td>
<td>□</td>
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</tr>
<tr>
<td>Parfym, hårspray m.m.</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Ilska glädje eller andra starka känslor</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Annat: _____________________________________________________________

8. Har du eller har du haft astma?

☐ Ja        ☐ Nej → Fråga 14

9. Har du av läkare fått diagnosen astma?

☐ Ja        ☐ Nej


11. Vilket år hade du senast astmabesvär? __________

12. Har du haft något astmaanfall under de senaste 12 månaderna?

☐ Ja        ☐ Nej

13. Har du någon gång de senaste 12 månaderna:

<table>
<thead>
<tr>
<th>Orsak</th>
<th>Nej</th>
<th>Ja, 1 gång</th>
<th>Ja, 2 gånger</th>
<th>Ja, mer än 2 gånger</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>□</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>b.</td>
<td>□</td>
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<td>c.</td>
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</tbody>
</table>

...sökt akut till vårcentral/husläkarmottagning på grund av att du blivit sämre i din astma?

...sökt akut till sjukhus på grund av försämring i din astma?

...legat på sjukhus på grund av din astma?
14. Har du någonsin varit besvärad av nysningar, rinnsnuva eller nästäppa utan att ha varit förkyld?
   ❑ Ja    ❑ Nej

15. Har du hösnuva eller någon annan allergisk snuva?
   ❑ Ja    ❑ Nej

16. Har du märkt att Du reagerar mot pollen med snuva, ögoninflammation eller hosta/andningssvårigheter?
   ❑ Ja    ❑ Nej

17. Har du märkt att Du reagerar mot pälsdjur med snuva, ögoninflammation eller hosta/andningssvårigheter?
   ❑ Ja    ❑ Nej

17 b. Om Ja, Skriv in vilket djur: ______________________________

18. Har du tagit snabbverkande luftrörsvidgande medicin, till exempel Bricanyl, Ventoline, Buventol eller Airomir, på grund av andningsbesvär mer än två gånger den senaste veckan?
   ❑ Ja    ❑ Nej    ❑ Vet ej

19. Har du tagit kortison för inandning, till exempel Pulmicort, Flutide, Becotide, Asmanex eller Beclomet, det senaste halvåret?
   ❑ Nej    ❑ I perioder    ❑ Regelbundet    ❑ Vet ej

20. Har du tagit långverkande luftrörsvidgande medicin, till exempel Serevent eller Oxis, det senaste halvåret?
   ❑ Nej    ❑ I perioder    ❑ Regelbundet    ❑ Vet ej

21. Har du tagit extra doser av långverkande luftrörsvidgande medicin, till exempel Oxis, på grund av andningsbesvär mer än två gånger den senaste veckan?
   ❑ Ja    ❑ Nej    ❑ Vet ej

22. Har du tagit Seretide eller Symbicort (kombination av långverkande luftrörsvidgande och kortison) det senaste halvåret?
   ❑ Nej    ❑ I perioder    ❑ Regelbundet    ❑ Vet ej

23. Har du tagit extra doser Seretide eller Symbicort mer än två gånger den senaste veckan?
   ❑ Ja    ❑ Nej    ❑ Vet ej
24. Har du tagit Singulair (tabletter) **det senaste halvåret**?
   - Nej
   - I perioder
   - Regelbundet
   - Vet ej

25. Har du på grund av astmaförsämring behövt ta kortisontabletter (Betapred eller Prednisolon) vid något tillfälle under **det senaste halvåret**?
   - Nej
   - Ja, en gång
   - Ja, vid 2 olika tillfällen
   - Ja, vid fler än 2 olika tillfällen
   - Använder kortisontabletter regelbundet

26. Var du hemma från skolan på grund av sjukdom minst 10 dagar under förra terminen?
   - Ja
   - Nej

26a. Om Ja, berodde det på infektioner eller någon form av luftrörsbesvär?
   - Ja
   - Nej

27. Har du någon annan sjukdom (utöver astma eller andra besvär från luftvägarna) som gör att Du träffar läkare eller annan vårdpersonal regelbundet?
   - Ja
   - Nej

27.b Om Ja vilken/vilka sjukdomar________________________________________________________________________________________

28. Har Du under någon period de senaste 12 månaderna regelbundet utövat någon fysisk aktivitet, förutom skolidrotten, som kräver hård ansträngning och gör att Du andas mycket snabbare än vanligt (t.ex. bollsporter, tävlingsdans, ridning, simning, orientering, gymnastik, skidåkning, friidrott)
   - Ja
   - Nej

28a. Om Du svarat Ja skriv:

<table>
<thead>
<tr>
<th>Typ av fysisk aktivitet</th>
<th>Antal gånger i veckan</th>
<th>Under antal månader</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>
29. Har du under någon period de senaste 3 åren regelbundet utövat någon annan fysisk aktivitet, förutom skolidrotten, som du inte tagit upp i fråga 28 och som krävde hård ansträngning och gör att du andades mycket snabbare än vanligt?

☐ Ja  ☐ Nej

29a. Om Du svarat Ja skriv:

<table>
<thead>
<tr>
<th>Typ av fysisk aktivitet</th>
<th>Antal gånger i veckan</th>
<th>Under antal månader</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

30. Har du under fysisk aktivitet eller direkt efter fått något eller några av följande besvär mer än en gång?

- väsande pipande andning
- tryck i bröstet
- svårt att andas/andnöd
- hosta
- större besvär att andas in än att andas ut
- att det är trångt i halsen
- kvävningsskänsla
- heshet
- ljud som bara hörs när Du andas in

Andra besvär Ange vilket/vilka: __________________________________________
____________________________________________________________________
___________________________________________________________________

<table>
<thead>
<tr>
<th>Stämmer in på mig</th>
<th>Stämmer inte in på mig</th>
<th>Vet ej</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mina besvär kommer framförallt medan jag anstränger mig.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Mina besvär kommer framförallt efter jag har ansträngt mig.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Det tar mindre än 5 minuter innan besvären startar när jag anstränger mig kraftigt.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Det tar mer än 5 minuter innan besvären startar när jag anstränger mig kraftigt.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Om jag fortsätter att anstränga mig kan jag få besvären att försvinna.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Om jag slutar anstränga mig försvinner besvären inom 5 minuter.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Besvären kommer tillbaka på samma sätt varje gång jag börjar anstränga mig kraftigt igen.</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Jag har hosta efter att de övriga besvären försvunnit</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Om jag har andats in luftrörsvidgande medicin (t.ex. Bricanyl eller Ventoline) får jag mindre besvär när jag anstränger mig.</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

32. Har besvären du markerat i fråga 30 varit orsak till att du slutat med eller bytt till en annan regelbunden fysisk aktivitet?

Fyller Du bara i om Du svarat Ja på något alternativ i fråga 30:
☐ Ja slutat ☐ Nej ☐ Har bytt

32a. Om Ja, jag har slutat med ____________________________

32b. Om Ja, jag har bytt till ____________________________

Slutligen två frågor om hur mycket Du är fysiskt aktiv.
33. Fysisk aktivitet är all aktivitet som får ditt hjärta att slå snabbare och som gör dig andfådd. Fysisk aktivitet kan man hålla på med i idrottssammanhang, i skolan, när man leker med kompisar eller när man går till skolan.

När du svarar på frågorna, lägg ihop all tid som du är fysiskt aktiv varje dag.

a. Hur många dagar har du varit fysiskt aktiv sammanlagt minst 1 timme om dagen under den senaste veckan?

☐ □ □ □ □ □ □ dag

□ □ □ □ □ □ □ dagar

b. Hur många dagar är du fysiskt aktiv sammanlagt minst 1 timme om dagen under en vanlig typisk vecka?

☐ □ □ □ □ □ □ □ dag

□ □ □ □ □ □ □ dagar

34. Hur lång är du? _____________cm

35. Hur mycket väger du? ________kg

Tack för att ni tog er tid att svara på frågorna!

Vissa personer som svarat på frågorna kommer att bli kontaktade igen.

36. Ni får kontakta oss igen

☐ Ja ☐ Nej

37. Om Ja, ange telefonnummer dit vi kan ringa:

Hem: __________________________

Mobil: _________________________

eller om ni föredrar att vi skickar ett e-mail

Ange mailadress ________________________________
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”.)