




# BMJ Open Prevalence and impact of exercise-induced laryngeal obstruction in asthma: a study protocol for a cross-sectional and longitudinal study

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## ABSTRACT

**Introduction** Exercise-induced laryngeal obstruction (EILO) and exercise-induced asthma can cause troublesome respiratory symptoms that can be difficult to distinguish between. Further, there is now a growing appreciation that the two conditions may *coexist*, complicating the interpretation of symptoms. The primary aim of this study is to investigate the prevalence of EILO in patients with asthma. Secondary aims include evaluation of EILO treatment effects and investigation of comorbid conditions other than EILO in patients with asthma.

**Methods and analysis** The study will be conducted at Haukeland University Hospital and Voss Hospital in Western Norway, and enrol 80–120 patients with asthma and a control group of 40 patients without asthma. Recruitment started in November 2020, and data sampling will continue until March 2024. Laryngeal function will be assessed at baseline and at a 1-year follow-up, using continuous laryngoscopy during high-intensity exercise (CLE).

Immediately after the EILO diagnosis is verified, patients will be treated with standardised breathing advice guided by visual biofeedback from the laryngoscope video screen. The primary outcome will be the prevalence of EILO in patients with asthma and control participants. Secondary outcomes include changes in CLE scores, asthma-related quality of life, asthma control and number of the asthma exacerbations, as assessed between baseline and the 1-year follow-up.

**Ethics and dissemination** Ethical approval has been obtained from the Regional Committee for Medical and Health Research Ethics, Western Norway, (ID number 97615). All participants will provide signed informed consent before enrolment. The results will be presented in international journals and conferences.

**Trial registration number** NCT04593394.

## INTRODUCTION

In recent years, laryngeal dysfunction has received growing recognition as a frequent, but often underdiagnosed, cause of dyspnoea. The label ‘exercise-induced

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ There will be used standardised continuous laryngoscopy exercise testing and a structured score system to rate laryngeal movements, allowing for best possible verification of a diagnosis of exercise-induced laryngeal obstruction (EILO).
- ⇒ The inclusion of a control group without asthma allows for comparison of EILO prevalence between patients with and without asthma.
- ⇒ The study’s primary limitations is a relatively small study sample; however, compared with previous studies in this area, the planned number of participants is large.
- ⇒ For the longitudinal substudy, the lack of a treatment control group is a limitation.

laryngeal obstruction’ (EILO) defines a condition characterised by adduction of glottic and/or supraglottic tissues, leading to a reduced size of the laryngeal inlet and, thereby, temporary partial obstruction of free airflow to the lungs.<sup>1</sup> EILO and asthma share several common symptoms; thus, it can be challenging to distinguish between the two. Although research on this subject is still at an early stage, studies using varying methodologies have consistently reported high but variable rates of laryngeal abnormalities coexisting in patients with asthma.<sup>2–7</sup> As EILO and asthma require fundamentally different approaches to treatment diagnostic mistakes may lead to harm.

Exercise is a common trigger for both exercise-induced bronchial obstruction (EIB) and EILO. The two conditions are diagnosed differently, with an EIB test or a continuous laryngoscopy exercise (CLE) test, respectively.<sup>8,9</sup> The CLE test has been conducted on few patients with asthma, as most of the individuals previously studied have been

young and otherwise healthy athletes, and few studies have specifically enrolled patients with asthma.<sup>7 10–14</sup> Thus, the prevalence estimates of EILO in the asthmatic populations remain uncertain. A systematic meta-analysis by Lee *et al* reported a pooled prevalence of all causes of induced laryngeal obstruction of 38% in patients with asthma,<sup>2</sup> whereas a recent systematic review in 2022 by Thomander *et al*<sup>15</sup> reported EILO in 13.5% of subjects who had an asthma diagnosis or a history of using asthma medications. Furthermore, we also have a limited understanding of how prevalent EILO is in the general population. Johansson *et al* examined 125 adolescents (mean age 14 years) with CLE tests and found evidence of laryngeal obstruction in 10.8% of participants who reported dyspnoea during exercise, and in 4.8% of those who did not report such symptoms.<sup>16</sup> Similarly, Christensen *et al* found laryngeal obstruction in 7.6% of their invited adolescents and young adults.<sup>7</sup> To further complicate this topic, the cut-off for what should be considered pathological laryngeal adduction has not been settled,<sup>17</sup> and various degrees of laryngeal adduction have repeatedly been reported in individuals who do not necessarily complain of respiratory problems during exercise.<sup>18 19</sup>

### Asthma control and asthma-related quality of life (QoL) in patients with EILO

Our understanding of how comorbid EILO impacts asthma control is hampered by few studies, with few participants and with conflicting results. Hull *et al* found similar asthma control scores in patients with normal and abnormal laryngeal function.<sup>3</sup> Similar findings were reported by Abdelwahab *et al*, with no differences in asthma control, irrespective of comorbid EILO.<sup>13</sup> Walsted *et al* found no relationship between comorbid EILO and asthma-related QoL.<sup>12</sup> Contradicting these studies, Parsons *et al* studied 59 patients with asthma and found decreased disease control in patients with comorbid glottic obstruction.<sup>20</sup>

### Treatment approaches for EILO

It remains unclear how treatment of comorbid EILO impacts asthma control and medication use, as this has never been systematically investigated. For EILO in general, the literature indicates that treatment with physiotherapy, speech–language therapy, inspiratory muscle training and supraglottic surgery can improve respiratory symptoms as well as laryngeal function.<sup>21–26</sup> At our department, as a first-line treatment for over 15 years, all patients with confirmed EILO receive breathing advice including visual biofeedback, performed by leaving the laryngoscope in place after the diagnostic testing while the patient is educated in breathing techniques. The method is relatively simple and leads in our experience to improvements of EILO symptoms in a majority of patients. Positive effects have also been documented in studies, although not within a randomised controlled design.<sup>23 27</sup>

### Other comorbidities and mimics of asthma and EILO

There is a considerably overlap between comorbid conditions in asthma and EILO. The negative impact on asthma control from several comorbid conditions is well documented.<sup>28–30</sup> In EILO, due to limited evidence, the impact of comorbid conditions is more uncertain.

Obstructive sleep apnoea (OSA) is reported to be common in asthma, and treatment of comorbid OSA in asthma has been reported to reduce exacerbation rates and enhance asthma control.<sup>31–35</sup> To our knowledge, there is no literature on OSA in patients with EILO.

Depression and anxiety are comorbid conditions in patients with asthma and seem to correlate with impaired asthma control and asthma-related QoL.<sup>36–41</sup> In EILO, the existing literature on anxiety and depression is conflicting. Our clinical experience is that fear and anxiety provoked by episodes of laryngeal closure may aggravate and prolong the patients' respiratory symptoms. Some older studies and case reports have reported high frequencies of psychiatric disorders and psychological triggers in patients with laryngeal obstruction.<sup>42–45</sup> However, these findings have not been confirmed in the more recent literature, and a recent study found no excess of anxiety symptoms when compared with normative data.<sup>46</sup> The complicated task of inferring causality between observations that appear to be associated is relevant in this context; that is, do psychological traits cause laryngeal abnormalities, or is it the other way around, that an uncontrollable choking feeling caused by laryngeal collapse challenges the 'balance of mind'?

Gastro-oesophageal reflux disease has been listed as a comorbid condition in both asthma and EILO.<sup>45 47–49</sup> The evidence on how treatment of comorbid gastro-oesophageal reflux impacts asthma control is conflicting.<sup>50–52</sup> Several other conditions might mimic EILO, such as laryngeal oedema, extra thoracic obstruction, dysfunctional breathing, laryngospasm, panic attacks, respiratory laryngeal dystonia, exertional dysautonomia, diaphragm flutter and respiratory dystonias.<sup>53</sup> Such mimics will be examined and diagnosed to the extent possible given the tools available within the frames of this study (spirometry data, exercise data and findings/observations recorded during CLE tests).

In summary, although several studies have reported high rates of EILO in patients with asthma, data in this area are still limited. It remains unclear whether comorbid EILO impairs asthma control, asthma treatment and asthma-related QoL. Furthermore, the occurrence as well as the impact of other comorbid conditions shared by both EILO and asthma are not well understood. The overall purpose of the current study is to contribute to a clarification of these issues. If successful, this project can alter the work-up of patients with asthma by introducing the larynx as a factor that needs to be considered and perhaps contribute to new approaches to treatment in patients with 'difficult to treat' asthma.

## Study aims

The primary aim is to estimate the prevalence of EILO in a hospital-based population treated for asthma compared with a control group without asthma. Baseline data will include key information on asthma control and asthma-related QoL, data that will be used as comparators in the follow-up section of this study. Further, in patients who are diagnosed with EILO, we aim to examine changes (first visit vs the 1-year follow-up) in CLE scores after treatment with breathing advice guided by visual biofeedback provided at the first visit shortly after the diagnosis of EILO is verified. Moreover, this study aims to evaluate changes (first visit vs the 1-year follow-up) of asthma control scores, asthma-related QoL scores and number of asthma exacerbations. Lastly, we will investigate the occurrence of non-EILO asthma comorbidities (ie, OSA, depression and anxiety, gastro-oesophageal reflux disease, sinonasal disease and obesity), and explore their distribution between participants with and without EILO.

## METHODS AND ANALYSIS

### Design and overall study flow

The study has two parts. The first part is a cross-sectional study, enrolling adult patients with asthma and a control group without asthma. This is followed by a prospective 1-year observational study. Following recruitment and obtaining written informed consent, all participants will attend two study visits with a 1-year interval. At both visits, participants with asthma will perform a CLE test, measure lung function and fill in standardised and validated questionnaires evaluating asthma control, asthma-related QoL and respiratory symptoms. The control participants will perform a CLE test at both visits, but not fill in the asthma-specific questionnaires. All participants diagnosed with EILO will be provided departmental standard first-line treatment for EILO.

At enrolment, demographic and clinical data from the preceding year will be collected by self-reports and by searches in the participants' medical records. We will record a detailed asthma history (such as the criteria used to diagnose asthma, respiratory symptoms, exhaled nitric oxide, s-eosinophils, frequency of exacerbations), data on medication use (including changes of asthma medication), non-EILO comorbidities (such as OSA, depression and anxiety, gastro-oesophageal reflux disease, sinonasal disease and obesity), life-long smoking history and data on allergies and atopy. At the second study visit, similar data will be collected for comparisons, again using self-reports and searches in the participants' medical records. Additionally, participants with asthma not previously examined for OSA will undertake a home respiratory polygraph recording for two nights.

### Study setting and eligibility

The study will take place at the Departments of Thoracic and Pediatric Medicine, Haukeland University Hospital, and Voss Hospital in Western Norway. The data sampling

period will be from November 2020 to March 2024. The study will include subjects 18–70 years, constituting two study groups; a group with adult patients with asthma and a control group of adult participants without asthma. Eligible participants with asthma presenting from November 2020 to October 2022 at the outpatient clinic at the Thoracic Department, Haukeland University Hospital and Voss Hospital will be invited to participate. A total of 80–120 participants with asthma will be recruited, of them 40–80 patients with Global Initiative for Asthma (GINA) severity step 5, and 40 patients with GINA steps 1–4. The diagnostic evaluations for asthma in this study will be performed by experienced pulmonologists, based on objective lung function testing supported by a compatible history, in accordance with the recommendations stated in the GINA guidelines.<sup>54</sup>

The control group will consist of 40 participants with no history of asthma and no history of respiratory symptoms compatible with asthma. The control participants will be consenting individuals recruited from the Clinic of Sleep Medicine in the Thoracic Department, Haukeland University Hospital. They will be patients referred to this clinic due to suspected sleep disorder (OSA or insomnia), but otherwise relatively healthy, with an age and gender distribution similar to the asthma group.

### Exclusion criteria

Exclusion criteria will be cancer in the lung, head or neck region, known laryngeal pathology, age over 70 or below 18 years, unstable asthma in the previous month, a history of life-threatening asthma episodes or other unstable medical conditions making subjects unfit for exercise testing, such as unstable cardiovascular disease, untreated severe hypertension, arrhythmias, orthopaedic or neurological diseases. Additionally, control participants will be excluded if they have spirometry findings below lower limits of normal.

### Sample size for prevalence estimates

To report the prevalence of EILO in patients with asthma using a 95% CI (Wilson's method) and a worst case of a 15% absolute margin of error, the study requires a minimum of 40 participants with asthma.

### Sample size of the control group

Based on previous reports,<sup>2 7 16</sup> we assume a prevalence of EILO of 38% and 7% in the asthma and control groups, respectively. To test for differences in prevalence, we will use the Fisher-Boschloo exact unconditional test modified by the Berger and Boos procedure with  $\gamma=0.0001$ , as recommended by Fagerland *et al.*<sup>55</sup> By using a significance level of 0.05, we will need 35 study participants in each group to achieve a 90% probability of detecting a difference in the prevalence of EILO between the groups. The assumed prevalence of EILO is uncertain, based on few studies with few participants. We also expect that approximately 5%–10% of the CLE tests will be tested failures/stopped before reaching maximal exercise and therefore

not valid. Thus, we plan to recruit 80–120 participants with asthma and 40 control participants without asthma.

### Matching

The control group will contain participants without asthma but similar to the asthma group participants with regard to age and sex. There will not be individual matching.

### Outcomes

#### Primary outcomes

The prevalence of EILO in patients with asthma versus in a control group without asthma measured at baseline at the first CLE test.

#### Secondary outcomes

Distribution of CLE scores at baseline and at the 1-year follow-up and changes in CLE scores from baseline to follow-up. Baseline values and changes from baseline to the 1-year follow-up of the asthma-related QoL questionnaire scores, asthma control test questionnaire scores and number of asthma exacerbations in patients with and without EILO. The frequencies of other baseline comorbid conditions (OSA, depression and anxiety, gastro-oesophageal reflux disease, sinonasal disease and obesity) in patients with versus without EILO.

#### Pulmonary function test

A spirometer of type Vyntus Pneumo (Vyaire Medical GmbH, Hoechberg, Germany) will be used to obtain forced expiratory volume in one second and forced vital capacity. Performance and calibration will be done as recommended in guidelines.<sup>56 57</sup> We will use the Global Lung Function Initiative reference equations.<sup>58</sup>

#### CLE test

The CLE test will be conducted in accordance with the test method originally developed by Heimdal *et al.*<sup>9</sup> The testing will be conducted on a treadmill (Woodway PPS 55MED, Weil am Rhein, Germany) starting flat with a speed of 1.5 km/hours and speed and inclination will increase every minute. Participants will walk and preferably run until reaching peak exercise or stopped by symptoms. Study participants with asthma will be premedicated with 400 µg of inhaled salbutamol 10–15 min prior to CLE testing. Local anaesthesia (lidocaine) will be applied directly in the nose, as well as a gel applied on the laryngoscope (Olympus ENF-P3, Tokyo, Japan). The laryngoscope with diameter 2.9 mm will be positioned in the epipharynx during exercise. To ensure a stable position while running, the laryngoscope will be fastened to a headgear and a facemask. The facemask ensures a closed system allowing measurements of gas exchange parameters via a connected cardiopulmonary exercise test system (Vyaire Medical). A standard 12-lead electrocardiogram (CUSTOMED, Custo Diagnostic, Germany) will be registered during the testing. During testing, the recordings of the larynx will be shown in real-time on a television screen. The CLE test will be approved if

the participants stop because of exhaustion or breathing difficulties, ideally also with achievement of a minimum of 80% of maximal predicted heart rate and/or a respiratory exchange ratio >1.10, and/or if there is a flattening in the curve for oxygen consumption indicating maximal exercise. CLE tests not achieving these criteria or CLE tests stopped by the investigators due to safety concerns will be regarded as inconclusive and reported separately.

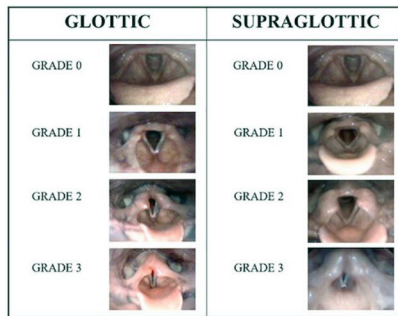
#### Breathing advice with visual biofeedback

Breathing advice with visual biofeedback will be performed as an integrated procedure in the CLE test and will be provided to all participants diagnosed with EILO. This method is the preferred first-line standard treatment of EILO at our department, and the full method was described in a recent protocol article.<sup>59</sup> The goal is to educate patients on optimal breathing patterns and body posture, and by this increase the patients' conscious control over their own laryngeal muscles, leading to less, or at least delayed, adduction of laryngeal structures during exercise.

Briefly, when the laryngoscope is correctly positioned in the larynx and before the exercise starts, all participants will receive standardised basic information about normal laryngeal anatomy and function and information on how laryngeal structures close during an EILO attack, while seeing the movements of their own larynx.

Directly after the participants have completed the CLE test, while the laryngoscope is still positioned in the larynx and the patient is experiencing an EILO episode, the patient will be provided with an explanation of how the laryngeal structures (as visualised on the video screen) adduct and obstruct the inlet to the 'air pipe'. Thereafter, when the EILO episode has ended, participants will be provided with standardised breathing lessons:

- Visual biofeedback: patients will observe and experience how different breathing patterns affect the movements of their laryngeal structures. First, patients will be instructed to provoke dysfunctional laryngeal movements by making a stridor noise and extensively use the upper thoracic breathing muscles. Thereafter, patients will be instructed to alter to normal breathing patterns with the use of diaphragmatic breathing muscles while not making stridor.
- Optimal postural position: the patients will observe and experience how an optimal body posture during breathing (head raised, shoulder muscles relaxed and the thoracic cage elevated) can serve to optimise the size of the laryngeal inlet.
- Enhancing diaphragmatic breathing: the patients will observe and experience how diaphragmatic breathing and avoidance of dysfunctional upper chest breathing patterns can serve to optimise the size of the laryngeal inlet.
- Education in techniques to terminate attacks of laryngeal obstruction: the importance of breathing slowly and avoidance of rapid, loud breathing will be highlighted. Moreover, patients will be educated in



**Figure 1** The Continuous Laryngoscopy Exercise Score grading. Permissions to reproduce obtained from Fretheim-Kelly *et al*, *Frontiers in Physiology*.<sup>75</sup>

different breathing techniques to stop an EILO attack, basically by means of slowing inspiratory flow through various techniques.

The participants will be provided with written information about all the different breathing techniques they have been informed of. All elements in this treatment session will be standardised to the extent possible.

### CLE test scoring

Laryngeal responses will be analysed from the video-recorded CLE test by two researchers blinded to the participant's clinical data. We will use the system developed by Maat *et al*,<sup>60</sup> where obstruction at supraglottic and glottic structures is scored at moderate and maximal exercise, with individual scores ranging from 0 to 3, where 0 is full opening and 3 is nearly complete adduction of the laryngeal inlet. EILO is considered present if there is a score of  $\geq 2$  at any level or effort. The total CLE Score is the sum of all four scores; that is, glottic and supraglottic scores at both intensities, with a theoretical maximum score of 12, see [figure 1](#).

### Severe asthma exacerbations

These will be defined by treatment with systemic glucocorticoids for minimum 3 days, in patients who do not use this medication on a regular basis, or a doubling of the regular systemic glucocorticoid dose in those who do, or a hospital admission due to an asthma exacerbation.<sup>61</sup> The number of severe exacerbations during the previous year will be counted both at enrolment and at the 1-year follow-up visit, with data obtained by self-reports and by searches in the electronic medical journal.

### Comorbid conditions other than EILO

The frequency of comorbid conditions in all participants will be defined by self-reports and searches in the participants' medical records. The frequency of participants with increased scores on the questionnaire indicating disease will also be reported, but a positive questionnaire screening will not be considered diagnostic for comorbid conditions.

### Respiratory polygraph recording diagnosing OSA

All participants with asthma not previously tested for OSA will have an at-home overnight respiratory polygraph recording (NOX-T3, Nox Medical, Iceland) for two consecutive nights with a standard set-up. The American Sleep Association guidelines will be used for definitions and scoring of apnoeas and hypopnoeas.<sup>62</sup> Two researchers will score the recordings manually, after initial software analysis. Participants will also answer a questionnaire about sleep duration during the nights of the recordings to exclude recording periods out of sleep phase.

### Questionnaires

#### Mini-Asthma QoL Questionnaire

A 15-item self-rated questionnaire measuring asthma-related QoL in patients with asthma. Each item has a range from one to seven (lower score indicate worse health related QoL), and the total score is calculated as an average of the items.<sup>63</sup>

#### Asthma control test

A self-rated five-item questionnaire measuring asthma control during the past 4 weeks. Each item ranges from one to five, and a sum score of  $>19$  indicates good asthma control.<sup>64</sup>

#### Hospital Anxiety and Depression Scale

A self-rated 14-item validated questionnaire measuring symptoms of depression and anxiety. Each item ranges from zero to three, and a sum score of  $\geq 8$  indicates an elevated risk of having anxiety and depression.<sup>65</sup>

#### STOP-Bang Questionnaire

STOP-Bang, a self-rated eight-item, questionnaire measuring the risk for having sleep apnoea, four items are regarding the symptoms of sleep apnoea and four objectives (body mass index  $>35 \text{ kg/m}^2$ , neck size  $>40 \text{ cm}$ , male sex and age  $>50$  years). A sum score of  $\geq 3$  indicates an elevated risk of having OSA.<sup>66</sup>

#### Sino-Nasal Questionnaire

A self-rated five-item questionnaire measuring symptoms and risk of having sino-nasal disease. Each item has a range from zero to three. A mean score of  $\geq 1$  indicates an increased risk of having sino-nasal disease.<sup>67</sup>

#### Gastroesophageal Reflux Disease Questionnaire

A self-rated six-item questionnaire measuring the risk of having gastro-oesophageal reflux disease. Each item ranges from zero to three points, and a total score of  $\geq 8$  points indicates an increased risk of having gastroreflux disease.<sup>68</sup>

#### EILO Questionnaire

A self-rated questionnaire measuring the extent of respiratory symptoms during exercise on scales from 1 (never) to 5 (always) and 0 (no complaints) to 10 (always).



## Statistical analyses

The prevalence of EILO in the study and control groups will be presented as frequencies and percentages with 95% CIs, calculated using Wilson's method. To test if there are differences in the prevalence of EILO between the study groups with and without asthma, we will use the Fisher-Boschloo exact unconditional test modified by the Berger and Boos procedure with  $\gamma=0.0001$ , as recommended by Fagerland *et al.*<sup>55</sup> Data will be presented with two-sided p values, and p values of  $\leq 0.05$  will be reported as statistically significant.

CLE scores are, by definition, ordinal (with a theoretical range from 0 to 12), but will also be presented as means with 95% CIs.<sup>69</sup> The CIs will be calculated using the percentile bootstrap with 9999 bootstrap replications.

Changes in the questionnaire scores from the first to the second assessment will be presented as means, SD and 95% CIs or as medians, quartiles and ranges, as appropriate. In the follow-up part of the study, we estimate approximately 20%–30% dropouts based on past trails.<sup>70–72</sup> Participants with improved laryngeal function might not see a personal benefit in attending a second CLE test; however, they may also want to confirm their sense of improvement. To handle missing data at follow-up, we will use mixed effects linear/ordinal/logistic models (which include baseline data for participants lost to follow-up) where appropriate.

Other comorbid conditions than EILO in the asthma cohort will be reported as frequencies with percentages, and for obstructive sleep apnoea, also by severity. The results will be reported stratified by EILO/non-EILO status, and we will also report percentage differences between the two groups, with 95% CIs.

A high CLE Score ( $\geq 2$ ) at baseline is an *inclusion criterion* for receiving treatment, which will result in a 'regression toward the mean' phenomenon if we examine change from baseline in CLE Score for treated individuals. (Even if treatment had no real effect, we would expect some reduction in CLE scores 'on average'.) In order to mitigate this, we will also report changes in scores for *all* patients, including those with no EILO (CLE Score  $< 2$  at baseline), using a mixed-effects ordinal model. The p value from this will provide a *conservative* test of the treatment effect, but will not be affected by the 'regression toward the mean' phenomenon.

The single primary outcome (ie, prevalence of EILO in patients with asthma vs in a control group without asthma) does not require adjustments for multiple comparisons. Analyses of the secondary outcomes are mainly explorative, and p values will not be adjusted for multiple comparisons.

## Patients and public involvement

Patient representatives have been actively involved in the project from the start. They have provided important input and influenced the development and focus of the project, as well as the choice of the methods that will be applied.

## ETHICS AND DISSEMINATION

Ethical approval has been obtained by the regional committee for medical research ethics in Western Norway (ID number 97615) (NCT 108266, registration date on 29 September 2020), and the study will be performed by the ethical standards of the Declaration of Helsinki and its later adjustments.<sup>73</sup> Informed signed consent statements will be obtained from all participants before inclusion. The results will be presented at local, national and international medical conventions, as well as in international peer-reviewed scientific journals. The results will also be presented on the project website<sup>74</sup> and via the patient organisations. The study protocol is registered at clinicaltrials.gov (NCT04593394). Data from all participants will be deidentified. Data files will be securely stored on a research data server. Our research group has extensive expertise in CLE testing,<sup>9 23 26</sup> which is considered a safe procedure for daily use in the hospital outpatient clinic. All adverse events will be recorded, and if any serious event occurs, the chief investigators will discuss and decide whether the study should be stopped or if other adjustments need to be made.

## DISCUSSION

Although the evidence is limited, studies have consistently reported a relatively high rate of EILO in asthma.<sup>2</sup> The results of this study will contribute to an enhanced understanding of the role of EILO in patients with asthma. Moreover, the study will also contribute to a better understanding of the role of comorbid conditions in asthma patients with versus without EILO. The present study has several strengths: the use of the CLE test will ensure a confirmed diagnosis of EILO in accordance with a task force recommendation issued by the European Respiratory Society, The European Laryngological Society and the American College of Chest Physicians,<sup>1</sup> and blinded assessment of the video-recordings will prevent biased conclusions to the extent possible. Further, this will be one of the first studies to explore the effects of treating comorbid EILO in patients with asthma while applying clinically important and validated outcome measures. This knowledge may lead to development of novel treatment avenues in patients with 'difficult-to-treat asthma', potentially saving society costs and patients from side effects from high doses of advanced pharmacological treatment with no effect on breathing problems caused by laryngeal obstruction. A relatively small sample size and, for the longitudinal substudy, the lack of a treatment control group and randomisation are the major limitations of the study. Studies with larger populations, potentially performed as controlled multicentre studies, should be conducted in the future to evaluate the effects of different treatment approaches for comorbid EILO in asthma.

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**Contributors** ÅJR, TMA, MV, SL, HHC, TH, KOH and ODR have planned the study and developed the study protocol. ÅJR, MV and HKK performed all the examinations in the study. All authors have contributed to the manuscript and approved it ahead of submission.

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**Competing interests** None declared.

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