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Development and Validation of the Exercise-Induced Laryngeal Obstruction Dyspnea Index (EILODI)

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PII: S0091-6749(21)01512-8

DOI: <https://doi.org/10.1016/j.jaci.2021.09.027>

Reference: YMAI 15298

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 23 March 2021

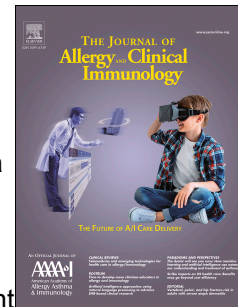
Revised Date: 6 September 2021

Accepted Date: 23 September 2021

Please cite this article as: Olin JT, Shaffer M, Nauman E, Durso CS, Fan EM, Staudenmayer H, Christopher KL, Gartner-Schmidt J, Development and Validation of the Exercise-Induced Laryngeal Obstruction Dyspnea Index (EILODI), *Journal of Allergy and Clinical Immunology* (2021), doi: <https://doi.org/10.1016/j.jaci.2021.09.027>.

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Declaration of interests

Outside of institutional affiliation, Dr. Olin is a respiratory consultant for the United States Olympic and Paralympic Committee and USA Swimming. He has also received honoraria from speaking at conferences for the American College of Sports Medicine and the Indiana Speech-Language and Hearing Association. None of the other authors hold perceived conflicts of interest.

Funding: This study was not externally funded.

Abstract

Background: Exercise-induced laryngeal obstruction (EILO) causes exertional dyspnea and is important for its effect on quality of life, diagnostic confusion with exercise-induced asthma, and healthcare resource utilization. There is not a validated patient reported outcome measure (PROM) specific to EILO.

Objective: To develop, validate, and define a minimal clinically important difference (MCID) for a PROM to be used with adolescents and young adults with EILO.

Methods: A multidisciplinary group created a preliminary measure, modified by a 10-member participant focus group, with 20 items scored along a 5-point Likert scale. A subsequent cohort of participants recruited from a clinic, aged 12-21 years, with confirmed EILO by continuous laryngoscopy during exercise testing 1) completed the measure at 3 points in time over 28 days, and 2) provided anchoring data in the form of a daily exercise log and categorical self-assessments of clinical improvement. Thirty additional participants without exertional dyspnea served as controls.

Results: Two hundred nineteen subjects with mild to severe EILO participated in the exploratory factor analysis, which identified seven factors within the preliminary outcome measure. After a process of item reduction, a 12-item metric with a total score ranging from 0-48 was developed. Mean scores of EILO patients and healthy controls at baseline were 28·8 (SD 7·4) and 4·5 (SD 7·4), respectively. A MCID of 6 was determined by comparison of index change with changes in categorical self-assessments of improvement.

Conclusion: This is the first PROM specifically designed for adolescents and young adults with EILO.

74 **Running Head:** EILODI: Patient-reported outcome measure for EILO

75 **Total word count for abstract: 245**

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Capsule Summary

The authors present the development and validation of the exercise-induced laryngeal obstruction dyspnea index (EILODI), the first patient-reported outcome measure created specifically for exercise-induced laryngeal obstruction.

Clinical Implications

The EILODI is a patient reported outcome measure to measure EILO symptoms across time, providing clinicians with a simple tool to assess response to therapies and researchers with a clinical trials outcome measure.

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Key Words: Exercise-induced laryngeal obstruction, EILO; Exercise-induced laryngeal obstruction dyspnea index, EILODI, Continuous laryngoscopy during exercise, CLE; Vocal cord dysfunction, VCD; paradoxical vocal fold motion; patient reported outcome measure, questionnaire

Abbreviations:

CLE: Continuous laryngoscopy during exercise
EFA: Exploratory factor analysis
EILO: Exercise-induced laryngeal obstruction
EILODI: Exercise-induced laryngeal obstruction dyspnea index
MCID: Minimum clinically important difference
PROM: Patient reported outcome measure
VCDQ: Vocal cord dysfunction questionnaire

Footnote: Preliminary data were presented at the 2018 American Speech-Language-Hearing Association Conference and the 2019 Global EILO meeting.

Introduction

Exercise-induced laryngeal obstruction (EILO) is a condition characterized by partial occlusion of the glottis or supraglottic structures during high-intensity exercise leading to episodes of respiratory distress, and was previously known as exercise-induced vocal cord dysfunction or exercise-induced paradoxical vocal fold motion.(1-3) It is common, estimated to affect 5-7% of the adolescent and young adult population, including elite athletes.(4-7) EILO impacts one's ability to exercise and is frequently misdiagnosed as asthma, leading to increased healthcare resource utilization.(8) The mechanism of this condition is poorly understood, with anatomic, micro-anatomic, environmental, and behavioral components postulated to contribute.(9, 10) In recent years, continuous laryngoscopy during exercise (CLE) has been proposed as the diagnostic gold standard.(11) Treatments for EILO include medical, surgical, and behavioral approaches.(12-15)

A major scientific gap in the study of EILO is the lack of a patient-reported outcome measure (PROM) specific to EILO. Subsequently, recent reports of potential therapeutic interventions for EILO have relied largely on non-validated patient self-report to assess intervention effectiveness.(16-18) Physiologic measures obtained at rest or during single episodes of exercise have not been shown to correlate with the impact of the condition during exercise or with CLE findings. (19, 20) Other potential markers of clinical status, including episodes leading to death or hospitalization, are unlikely and therefore not suitable for use in clinical trials. For these reasons, a need exists to develop a PROM to support clinical trials of treatment for EILO and to provide clinicians with a simple tool to assess change in clinical status over time.

There are two published PROMs that have been used in the assessment of upper airway dyspnea, the Dyspnea Index (DI) and the Vocal Cord Dysfunction Questionnaire (VCDQ)(21-23). These metrics were not designed to assess symptomatology in relation to exercise. A metric devoted to documenting the overall impact of dyspnea, specific to exercise will aid clinicians caring for patients diagnosed with EILO. The goal for this study was to develop and validate a new PROM, the Exercise-Induced Laryngeal Obstruction Dyspnea Index (EILODI) specifically designed to assess changes over time in participants with confirmed EILO. This study presents the methodology behind item creation including a theoretic framework, validation of the PROM, and minimal clinically important difference (MCID) with which to evaluate responses. (24)

Methods

Participants

This study was initially approved by the National Jewish Health Institutional Review Board and later transferred to the Biomedical Research Alliance of New York Institutional Review Board. All validation participants were recruited from the National Jewish Health Exercise and Performance Breathing Center from early 2016 to early 2018 after completion of continuous laryngoscopy during exercise testing performed for exertional dyspnea evaluation, judged to have at least mild glottic obstruction (anterior adduction of rima glottides) or moderate supraglottic obstruction (medial rotation of cuneiform tubercles with exposure of lateral mucosa).(11, 25) Controls were recruited from the community from December 2020 to January, 2021. All participants provided informed consent, as well as assent when appropriate.

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155 *EILO theoretic framework*

156 The process of PROM creation (figure 1) started with the development of a theoretical
157 framework for understanding symptoms. Specialists from adult and pediatric
158 pulmonology, allergy/immunology, otolaryngology, speech-language pathology, general
159 and performance psychology, sports medicine, respiratory therapy, and nursing
160 convened to create a theoretic framework of disease domains to be represented in a
161 PROM. The group reviewed literature, analyzed available metrics, and consulted with
162 clinicians who specialize in EILO, patients with EILO, and their parents to identify
163 relevant symptoms and general themes. Four a priori domains relating symptoms to 1)
164 physical; 2), episodic emotional, 3) chronic emotions, and 4) performance captured
165 most of the identified symptoms and themes.

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167 *Devising metric items*

168 The group contributed metric items considering the theoretic framework, items within
169 available metrics, and informal measures used in the literature to assemble 164 items
170 which reduced to 71 based on initial theme similarities by consensus. Items were
171 constructed to fit a unipolar five-point Likert scale, with higher values on the Likert scale
172 correlated with higher symptom burden, and without a clearly defined neutral response
173 or graphical representations of choices. Items were then optimized from the specific
174 perspectives of face validity, readability, ambiguity, value-laden terms, and negative
175 wording.(26) Consensus discussions narrowed the pool of items to 20 specifically
176 valuing the concepts above.

Subsequently, a focus group of three unblinded mediators (specialists in pulmonology, speech-language pathology, and behavioral health) and 10 patients, previously diagnosed with EILO via CLE, examined the EILO theoretic framework and concepts which they felt should be represented in a metric. The focus group evaluated the framework domains and PROM item readability, metric content, content absence, and a REDCap electronic data capture tool, and this feedback was incorporated into a new 20 item metric which was later subject to validation.(27)

Participants

Subjects, aged 12-21 years, recruited from a clinical pool of patients after CLE testing, regardless of asthma status (defined by prior documentation in the clinical record of a 12% improvement in forced expiratory volume in 1 second after bronchodilator administration or methacholine provocation concentration of less than 8 mg/ml), validated metric items. The target number of subjects was 200, or 10 times the number of PROM items.(28) Inclusion criteria required subjects to have at least mild glottic adduction or moderate supraglottic obstruction during high intensity exercise and self-identification that characteristic field symptoms were produced in the testing environment.(25)

Item validation and reduction

Each participant was asked to complete the 20 items at 3 points in time over one month (days 0, 14, and 28). Two subsets of subjects provided data for test-retest reliability of both individual PROM items and the anchoring daily log by re-taking the 20 item metric pool (24 hours after initial submission, n=55) and daily exercise log (12 hours after initial

submission on each of 2 consecutive days, n=39 subjects, 61 test-retest pairs), respectively (figure 2). To anchor the metric and establish a MCID, participants also completed a daily exercise log and two categorical self-assessments of 1) perceived recent improvement and 2) placement on a 4-tiered functional scale considering both condition and treatment burden (table 1). These were completed at days 0, 14, and 28.

Interventions

Treatment interventions were not rigidly standardized across the subject pool for the duration of the metric validation process as this study was not focused on treatment efficacy. Reasons for treatment variability reflected the realities of clinical medicine and included issues related to the subject (self-assessment of condition impact, motivation, tolerance of potential therapies, and availability) treatment center (staff and procedure availability, variability in expertise across providers) and advances in the field related to evolving therapies. Subjects were offered respiratory retraining which occurred with our speech-language pathology team and/or a respiratory team with expertise in therapeutic laryngoscopy during exercise.(15, 29) When deemed clinically appropriate, subjects were treated for asthma, allergic rhinitis, gastroesophageal reflux, nasal disease, and behavioral health concerns.

Analysis

Descriptive statistics were used to evaluate demographic and clinical features of subjects. Individual item reliability was assessed using a simple correlation and threshold below 0.7 for item exclusion. Exploratory factor analysis (EFA) identified factors of items, within which to reduce metric items.(28) Bias-corrected and accelerated bootstrap intervals quantified confidence around correlations between the

PROM and anchor metrics.(30) Means and standard deviations described PROM scores for the overall participant group, for subsets of participants, and for time periods characterized by clinical response or non-response based on categorical self-assessment, whose data determined the MCID.

Results

Participants

The 10 focus group participants (ages 12-21 years, 7 female, 8 Caucasian, 1 African American, 1 Caucasian Hispanic) spanned a spectrum of athletic level and participation from recreational to collegiate and did not participate in later metric validation. In addition to the focus group, demographic and clinical characteristics of subjects who subsequently participated in metric validation (n=219) are presented, including 49 subjects with co-existing asthma (table 2). Control groups included 30 subjects without asthma or complaints of exertional dyspnea.

Index changes based on focus group feedback

Focus group participants reviewed and discussed preliminary items. In addition to some semantic changes which slightly affected item number, items were specifically removed and other items were introduced. For reasons related to content, the following item was removed as it was unanimously felt to be irrelevant by the group participants: "During exercise, my breathing problem prevents me from enjoying exercise." Also related to content improvement, the following items were added: "I think about quitting my sport(s) because of my breathing problem," "during exercise, my breathing problem

makes it difficult to think clearly,” and “if my breathing problem occurs during exercise, I am disappointed in myself.”

Data integrity and completeness

Of the 219 enrolled, 201 completed the metric at least 1 point in time, reaching the target enrollment for index validation (figure 1). A subset of 55 completed it on both dates required to assess reliability. Individual items were designed to capture EILO symptom impact over a 2-week period and each of the 219 subjects in the study evaluated symptoms over 2 periods (four consecutive weeks) for a total of 438 possible periods of evaluation. Two hundred seventy-eight distinct 2 week periods were characterized by PROM completion at the beginning and end of the period, with 275 characterized by the additional completion of categorical assessment anchor data (required for determination of the MCID), and 264 of those periods were characterized by completion of additional anchoring data with daily symptoms logs on 2 of 3 days at both the beginning and end of the period (required for PROM anchoring to other assessments).

Data reliability and internal validity

Of the 20 metric items evaluated, 18 were characterized by a correlation of 0.7 or greater (table 3). When evaluating item responses between subjects with mild visualized glottic adduction and those with moderate or severe glottic adduction on CLE, there was only one item with a significant difference in the mean response. All questions were assessed for potential response differences between participant groups

with either mild or moderate to severe EILO, based on CLE assessment. Item 10, "When I exercise, my breathing is noisy" was acknowledged less frequently in patients with mild visualized glottic adduction than in those with moderate or severe adduction ($p<0.0001$). In terms of internal consistency, the mean response to single metric items across all subjects decreased over 28-day evaluation period for all metric items (table 3).

Exploratory factor analysis solution

EFA determined that a model of at least 7 factors prevented loss of significant information ($p=0.22$) whereas significant information was not retained in a 6 factor model ($p=0.04$). A single factor in a promax rotation was heavily represented in the preliminary metric, with 7 individual items (appearing to represent physical symptomatology) weighing most heavily in this factor.

Item reduction

Item reduction within identified factors occurred via interdisciplinary group consensus, valuing reliability, representation of all factors, symptom acknowledgement at the time of diagnosis, and the ability to change over the course of the evaluation period. Notable reductions included items 5 and 6, representing ideas about exercise avoidance and quitting, as they were rarely acknowledged even at the time of diagnosis. The final product is a 12-item metric now titled the Exercise-Induced Laryngeal Obstruction Dyspnea Index, or EILODI (table 4).

External validity

The mean score of all subjects with EILO was 28.8 (SD=7.4) with a median score of 29, from a possible total of 48. This compares to a mean of 4.5 (SD=7.4) in controls without respiratory disease ($p<0.0001$). To anchor the metric and assess an ability of the metric to change over time, the EILODI was compared with categorical assessments of disease burden and a daily log of symptoms (table 1). Across subjects completing these measures (at least 2 of 3 days in the daily log at each time point) at a given time point, there was significant correlation of the EILODI with the CDSA. Bootstrapping the sample based on the respondent number in order to model repeated measures produced a 95% bias-corrected and accelerated interval of (0.52,0.64). The same bootstrapping procedure applied to EILODI and spells/session resulted in a 95% bias-corrected and accelerated interval of (0.33,0.49). (figure 3). The mean score of subjects who only completed the EILODI at a single point in time upon study entry was 29.5 (SD=6.8).

Normative values

Although the metric was not designed to screen EILO patients from normal controls, given the baseline mean symptom scores and standard deviations noted above in EILO participants, it is reasonable to state that most symptomatic EILO patients presenting for evaluation will have total EILODI scores of 14 or greater.

Minimal clinically important difference

To assess the concept of MCID, responses to a binary categorical assessment asking about a significant clinical improvement were compared to EILODI changes across the period (table 1). A 2-week period was categorically characterized by either participant improvement (response period, $n=143$) or lack thereof (non-response period $n=132$) based on the response to the binary question. While assessing these periods, mean baseline EILODI score was 25.4 (SD=8.0) in response periods and 26.2 (SD=9.1) in non-response periods ($p=0.49$). Response periods were characterized by a mean EILODI improvement of 5.7 (SD=6.2) and non-response periods by a mean EILODI improvement of 1.9 (SD=5.7, $p<0.0001$).

To assess whether the change in EILODI scores was qualitatively similar across the spectrum of symptom severity when anchored to a 4-tiered categorical assessment of symptom burden, EILODI change was assessed in periods characterized by single increment steps in the 4-point categorical assessment (table 1). For subjects self-identifying, between days 0 and 14 or between days 14 and 28 (or both if change was noted in both time periods), with step-change improvements to points of 1) initial symptom improvement, 2) near-total symptom control with notable treatment burden, and 3) resolution of symptoms, the corresponding EILODI score changes across the periods were 5.1 (SD = 5.2, $n = 33$), 6.9 (SD 6.1, $n = 16$), and 7.6 (SD = 2.2, $n = 5$) units respectively. The authors determined that the most appropriate MCID was 6 based on the combination of EILODI change when anchored to both the binary categorical measure and to incremental step changes in the 4-tiered categorical measure. A

repeated measures analysis was not performed on this data given that only 3 subjects described consecutive single point step changes in the CDSA.

Influence of coexisting asthma

To assess the impact of asthma on the EILODI score, we compared the EILODI scores of those with physiologically documented asthma in addition to EILO with subjects with isolated EILO. When evaluating individual EILODI item responses between those groups, only the item which asks respondents to quantify the duration of episodes was statistically different across groups. Those with asthma and EILO indicated longer duration of events than those with isolated EILO ($p=0.03$). In scoring the entire metric, the asthma group had a mean baseline score of 27.3 (SD= 6.2) and non-asthma group had a mean baseline score of 25.4 (SD 7.0, $p=0.10$). The presence or absence of asthma was also evaluated in terms of its effect on response to therapy. Participants with asthma indicated improvement on the binary categorical assessment in 60% of periods compared to a rate of 50% in participants without asthma ($p=0.16$). Mean EILODI scores improved by 5.5 and 1.8 in patients with asthma who self-identified response periods versus non-response periods, respectively. In the subset of subjects without asthma, the mean EILODI improvements during response and non-response periods were 5.8 and 1.9, respectively.

Discussion

The EILODI is the first PROM specifically designed for EILO. This report describes a theoretic framework, process of item development, test properties of proposed items,

relationship with anchors of disease severity, and the MCID. Its validation was based on a large cohort of subjects. The EILODI demonstrated change over time which tracked with external anchors of disease assessment, and did not change excessively across asthma status.

Intended application of the EILODI

The EILODI was created to track changes in EILO symptoms and impact over time. The EILODI is intended to be a primary outcome for clinical trials of therapeutic interventions, as well as a useful clinical aid to assess response to EILO interventions. In settings reliant on clinical diagnosis of EILO, the EILODI can provide data to help evaluate response to therapy or change in symptom intensity. The absence of change in temporal proximity with appropriate therapeutic care could suggest therapy non-responsiveness or an alternative diagnosis. The EILODI was not designed or tested to screen subjects in a general or specialty population for EILO.

Strengths in metric creation process

There were several features of the process which should add strength to the EILODI. First, input from EILO patients, parents, and specialists from 10 different areas of medicine led to a very broad perspective on the experience of EILO in the construction of a theoretic framework construction and items. Secondly, the focus group, which featured representative patients was designed to capture perspectives across gender, age, race and ethnicity. Next, the EILODI is the first metric which was validated exclusively by subjects who were definitively diagnosed via the use of continuous

laryngoscopy during exercise. Moreover, the number of participants included in this study represents one of the largest cohorts of individuals with CLE-confirmed EILO reported in the literature and was sufficient to meet methodological psychometric guidelines for measurement.(28) Finally, the data were validated through anchoring to a daily log and separate categorical assessments, which provided a different type of quantitative data and allowed for calculation of the minimal clinically significant difference. (24)

Theoretic framework

The theoretical framework of symptoms was specifically designed to capture areas identified as important by patients, families, and providers. These areas (physical symptoms experienced during episodes, emotional symptoms experienced during episodes, chronic emotional consequences, and performance consequences) were identified as distinct factors in the EFA. Three other factors were statistically evident as the analysis subdivided physical symptoms into two factors, one capturing the sensation of dyspnea and the other related to secondary symptoms (muscle fatigue, lightheadedness, confusion). The factor related to exercise performance also seemed to subdivide into clusters related to process (taking extra breaks), results (slowing down and not meeting expectations), and activity avoidance. Items linked to each of the 7 domains were included in the final 12-item metric.

There are two specific concepts which are not represented in the metric that deserve attention for distinct reasons. First, the concept of exercise enjoyment, and the lack

thereof during episodes of exertional dyspnea, was hypothesized to be important by healthcare providers and investigators. This, however, was unanimously and strongly rejected by our focus group which felt that exercise served different purposes among adolescents. This was a surprising finding for the investigators and was subsequently discussed with other clinical patients to verify the opinion. Although individual patients occasionally acknowledged a clear link between exercise and enjoyment, its overall dissociation in these discussions was frequent enough for us to omit it from the metric. In an older population, this finding might be different. Secondly, the concept of quitting sporting activities was also hypothesized to be critical by providers, investigators, and the focus group. It has been used in other studies as a measure of intervention effectiveness.(18) However, our data suggested that, at least among clinical patients, the phenomenon is rarely acknowledged even at the time of diagnosis. For this reason, quantitating the presence of this phenomenon in a metric designed to track changes over time was not appropriate due to an apparent ceiling effect.

Asthma and the EILODI

Forty-nine of the validation subjects were physiologically demonstrated to have coexisting asthma at baseline. Interestingly, the presence or absence of asthma did not notably affect either the baseline EILODI values or change over time. The authors feel that this is a strength of the PROM when used to assess symptom burden in patients who are definitively diagnosed with EILO. A possible explanation for this finding is that many individuals with EILO and asthma can distinguish the cause of exercise-induced symptoms such that the score on the EILODI is not significantly impacted by the

presence or absence of asthma. It is also possible that more study is needed, given that the validation of the EILODI is based on anchoring to other measures of symptoms which themselves have not been tested against changes in spirometry or airway reactivity in field settings.

Caveats and limitations to the data

A few limitations to this report should be considered when relying on the use of this PROM and data. First, for reasons related to recruitment optimization, we decided to include subjects with grade 1 glottic obstruction if the clinical history, including described time course of symptom onset and symptom resolution, was consistent with previously published literature.(16, 25) We note the uniformity in responses between subjects with mild obstruction and those with more severe obstruction as support for the decision to include these subjects. Secondly, a narrow age range, from 12-21, was used. It is possible that clinical patients of other ages could value concepts or relate to symptoms differently than adolescents and young adults. Thirdly, this study took place at a single center, and despite the national referral base, most subjects were local. It is possible that clinical patients in other locations nationally or internationally might relate to symptoms differently. Fourth, only 63% of the participants submitted a complete anchoring dataset. It is possible that this response rate had a small effect on the data used to determine MCID. Fifth, the team of moderators for the focus group were not blinded and could have introduced bias in item discussion. Finally, the demographic breakdown of study subjects was not reflective of the demographic breakdown of society in general, including our local population. The female predominance noted in our cohort is a finding that has been reported previously in the literature. The race and

ethnicity distribution of our cohort is notable for the paucity of African American and Hispanic subjects. Although the included subjects reflected our referral population, the reason for the distribution remains unclear. It is possible that social determinants contributed to this distribution in our cohort. We acknowledge that the underrepresentation of African American and Hispanic subjects in our cohort could have affected the distribution of data and will investigate the reasons behind the referral bias.

Future directions

Moving forward, there are a few relevant directions to consider within the scientific community. First, it is reasonable to consider clinical trials of interventions for this condition now that a validated PROM, specific to exercise exists. While there are still challenges to standardizing diagnostic criteria, it is now possible to measure a response to interventions in a prospective manner. Second, with proper future validation, it is reasonable to consider extending the use of this or a related metric to other populations. EILO can occur in patients above the age of 21 and in those who speak languages other than English. Although the process of metric validation cannot be bypassed in extending the use of a metric beyond its tested demographic, the theoretic framework of symptoms provides a starting point for other investigators.

Conclusion

In conclusion, the 12-item EILODI is the first PROM specifically designed to track changes in symptoms and symptom impact in patients with EILO. It may be used in clinical trials with a suggested MCID of 6.

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475 **Acknowledgments**

476 The authors acknowledge the contributions of those who helped design metric items
477 including Bruce Bender, Allan Bock, Matthew Clary, Emily Deardorff, Valerie L. Keever,
478 Juliana Litts, Michael Morris and the team that helped with regulatory administrative
479 support including D Sundstrom, Michael White, Stephanie Jump, Lisa Kingsley, and
480 Mikalyn Johnson. The authors also thank and remember Kristina Johnston, a heavily
481 involved speech-language pathologist, who passed away prior to publication of this
482 manuscript.

483 **Role of the funding source:** This work was not externally funded.

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Figure Legends

Figure 1. Development process of theoretic framework and EILODI metric validation

Figure 2. Timeline of EILODI validation and anchoring. Figure legend: Two subsets of subjects tested item reliability on the EILODI (n =55) and daily log (n = 39 with 61 total responses over 3 days), respectively.

Figure 3. Changes in EILODI and anchor data across time. EILODI scores paralleled anchoring data in the form of respiratory episodes per exercise session and categorical assessment on a four-tiered scale when averaged across all subjects. Closed circles represent the EILODI score. Closed squares represent episodes of respiratory distress per exercise session. Closed triangles represent scores on the categorical assessment. Error bars represent standard deviations. Subject numbers per response appear below each data point. Regarding correlation, the 95% bias corrected and accelerated bootstrap interval applied to EILODI and the categorical assessment was (0.52,0.64). The interval applied to EILODI and spells/session resulted was (0.33,0.49)

Table 1. Anchoring metrics: Categorical assessments of improvement and function and daily log questions.

Table 2. Subject demographics and clinical features

Table 3: Reliability and validity measures of individual preliminary metric items.

*All items were scored with a 5-point Likert scale; † item 1 response choices: 0 = never, 1 = less than half of the time, 2 = about half of the time, 3 = most of the time, 4 = every time; ‡ item 2 response choices: 0 = 0 minutes, 1 = 1-3 minutes, 2 = 4-6 minutes, 3 = 7-10 minutes, 4 = more than 10 minutes; § item 3 response choices: 0 = not present, 1 =

mild, 2 = moderate, 3 = severe, 4 = extreme; 11 items 4-20 response choices: 0 = never,
1 = almost never, 2 = sometimes, 3 = almost always, 4 = always

Table 4: Exercise- induced Laryngeal Obstruction Dyspnea Index

Author contributions:

James Tod Olin was responsible for the study inception, study design, questionnaire item creation and revision, data acquisition, data processing, and data analysis. He wrote the first draft of the manuscript and compiled all author revisions.

Monica Shaffer was responsible for study design, questionnaire item creation and revision, and manuscript revision.

Emily Nauman was responsible for study design, questionnaire item creation and revision, and manuscript revision.

Catherine S. Durso was responsible for data analysis and statistics.

Elizabeth Fan was responsible for recruiting and manuscript revision.

Herman Staudenmayer was responsible for study inception, study design, questionnaire item creation and revision, and manuscript revision.

Kent Christopher was responsible for study inception, study design, questionnaire item creation and revision, and manuscript revision

Jackie Gartner-Schmidt was responsible for study design, questionnaire item creation and revision, and manuscript revision.

Categorical binary assessment of improvement

Do you feel that your breathing problem significantly improved in the last 2 weeks? (yes/no)

Categorical tiered assessment of improvement

Please indicate which set of statements most closely describes your current breathing symptoms:

0- I am almost always able to control my breathing during exercise. The breathing techniques that I use are not a burden.

1- I am often able to control my breathing during exercise, but the breathing techniques that I use are a burden.

2- I have breathing problems during exercise. The breathing techniques that I try to use help my breathing return to normal faster than doing nothing at all.

3- I have breathing problems during exercise. The breathing techniques that I try to use do not seem to help my breathing return to normal faster than doing nothing at all.

Daily symptom log

Did you exercise today?

How many separate times did you exercise today?

How long (total) did you exercise today?

How many episodes of shortness of breath did you experience?

	EILO (n = 219)	Controls (n = 30)
	n (%)	n (%)
age (mean, SD)	15.3 (1.9)	16.4 (3.6)
gender (female, %)	175 (80)	16 (53)
race and ethnicity (n, %)		
Causasian non-Hispanic	172 (79)	21 (70)
Causasian Hispanic	16 (7)	0 (0)
Causasian ethnicity unknown or unreported	8 (4)	2 (7)
Native American	2 (1)	0 (0)
Asian	3 (1)	4 (13)
African American	3 (1)	0 (0)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)
More than one race	13 (6)	3 (10)
Unknown or unreported	2 (1)	0 (0)
Athletic level (n, %)		
recreational	28 (13)	7 (23)
competitive below junior varsity level	44 (20)	4 (13)
junior varsity	37 (17)	2 (7)
varsity	96 (44)	7 (23)
collegiate	13 (6)	10 (33)
professional	1 (0)	0 (0)
EILODI score at baseline (mean, SD)	28.8 (7.4)	4.5 (7.4)
Continuous laryngoscopy during exercise, peak exercise glottic severity (n, %)		
grade 1	54 (25)	
grade 2	122 (55)	
grade 3	43 (20)	
Physiologic asthma diagnosis (n, %)	49 (22)	
Baseline FEV1, GLI 2012 (% predicted, SD)	99.5 (17)	
FeNO (n, SD, 161 available samples)	25 (29)	
≥1 aeroallergen positive (n, %, 114 tests)	85 (75)	

Item number	item stem	Test-retest correlation	domain number	Median score on day 0	mean change across 28 days
1	In the past 2 weeks when I exercised really hard, my breathing problem occurred *†	0.72	1	3	-0.73
2	In the past 2 weeks when I exercised really hard, my breathing problem typically lasted ____ minutes once I stopped. ‡	0.71	1	2	-0.50
3	In the past 2 weeks when I exercised really hard, my breathing problem was §	0.61	1	2	-0.51
4	I avoid really hard exercise because of my breathing problem.	0.87	2	1	-0.45
5	I avoid competitions because of my breathing problem.	0.93	2	0	-0.33
6	I think about quitting my sport(s) because of my breathing problem.	0.84	2	0	-0.23
7	I am nervous about my breathing problem before I exercise.	0.90	6	2	-0.57
8	If my breathing problem occurs during exercise, I am disappointed in myself.	0.80	5	2	-0.39
9	When I exercise, my throat feels tight.	0.79	1	3	-0.31
10	When I exercise, my breathing is noisy.	0.83	1	3	-0.43
11	When I exercise, I cannot get enough air in.	0.77	1	3	-0.57
12	When I exercise, I do not have control of my breathing problem.	0.77	1	2	-0.71
13	During exercise, my breathing problem makes me slow down.	0.70	3	3	-0.50
14	During exercise, my breathing problem prevents me from performing how I want.	0.72	3	3	-0.74
15	During exercise, my breathing problem makes my muscles feel tired.	0.77	4	2	-0.42
16	During exercise, my breathing problem frustrates me.	0.80	5	3	-0.86
17	During exercise, my breathing problem causes me to take extra breaks.	0.70	7	3	-0.60
18	During exercise, my breathing problem makes me feel lightheaded.	0.81	4	2	-0.69
19	During exercise, my breathing problem scares me.	0.83	6	2	-0.92
20	During exercise, my breathing problem makes it difficult to think clearly.	0.61	4	2	-0.45

Instructions: This is a questionnaire for patients that have breathing problems during exercise caused by the voice box. Please complete the following questions without the assistance of parents **considering the past 2 weeks**.

In the past 2 weeks when I exercised really hard,

my breathing problem occurred

Score:___

0 = never

1 = less than half of the time

2 = about half of the time

3 = most of the time

4 = every time

my breathing problem typically lasted ___ minutes once I stopped.

Score:___

0 = 0 minutes

1 = 1-3 minutes

2 = 4-6 minutes

3 = 7-10 minutes

4 = more than 10 minutes

For the rest of the items, please use the following scoring:

0 = never

1 = almost never

2 = sometimes

3 = almost always

4 = always

I avoid really hard exercise because of my breathing problem.

Score:___

I am nervous about my breathing problem before I exercise.

Score:___

When I exercise,

my throat feels tight.

Score:___

my breathing is noisy.

Score:___

I do not have control of my breathing problem.

Score:___

During exercise, my breathing problem

prevents me from performing how I want.

Score:___

frustrates me.

Score:___

causes me to take extra breaks.

Score:___

makes me feel lightheaded.

Score:___

scares me.

Score:___

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Total:___

