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Triggers of Breathlessness in Inducible Laryngeal Obstruction and Asthma

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

Running head: Triggers in ILO and Asthma

ABSTRACT

Background: Inducible laryngeal obstruction (ILO) is often misdiagnosed as, or may coexist with, asthma. Identifying differences in triggering factors may assist clinicians to differentiate between the two conditions, and could give mechanistic insights.

Objective: To identify and compare patient-reported triggers in ILO and asthma.

Methods: This was a two-part study. Initially we conducted a retrospective case note review of the triggers of ILO from endoscopically-confirmed ILO patients to generate a Breathlessness Triggers Survey (BrTS). Triggers were categorised as: scents, environmental factors, temperature, emotions, mechanical factors and daily activities. Secondly, ILO and/or asthma patients completed the BrTS prospectively, rating the likelihood of each item triggering their symptoms using a five-point Likert scale (strongly disagree to strongly agree). Chi-square testing was performed to compare responses by cohort.

Results: Data from 202 patients with ILO [73% female, mean (SD) age 53(16) years] were included in the case note review. For the prospective study, 38 patients with ILO-only [63% females, age 57(16) years], 39 patients with asthma-only [(56% female, age 53(13) years] and 12 patients with both ILO and asthma [83% female, mean age, 57 (14) years)] completed the BrTS. The triggers identified in the case note review were confirmed in the independent sample of patients with ILO and/or asthma and identified several difference in prevalence of the triggers between disease types. Mechanical factors [talking ($p<0.001$), shouting ($p=0.007$) and swallowing ($p=0.002$)] were more common in the ILO cohort compared to patients with asthma. Environmental factors [pollen/flowers ($p=0.005$) and damp air ($p=0.012$)] were more common in asthma. There were no differences between groups in frequency of reporting scents as triggers (except for vinegar, more common in ILO, $p = 0.019$), temperature, emotions or daily activities.

Conclusion: There were notable differences between patient-reported triggers of ILO and asthma, which may support clinician differential diagnosis.

INTRODUCTION

Inducible laryngeal obstruction (ILO) is an umbrella term for a group of conditions associated with acute breathlessness caused by episodic airflow obstructions arising in the larynx, most commonly manifesting as paradoxical adduction of glottic and/or supraglottic folds during inspiration, often referred to as vocal cord dysfunction [1]. This paradoxical adduction of glottic and/or supraglottic folds results in marked reduction in airflow through the larynx, producing distressing symptoms of dyspnoea, stridor, throat tightness and globus pharyngeus.[2-4]
A recent systematic review highlighted ILO as a comorbidity in quarter of asthma cases where ILO was identified by visualisation of laryngeal movement, with the value increasing to over one third when the ILO diagnosis included a provocation stimulus.[5] Further, in two prospective studies, of difficult-to-treat asthma and where ILO was suspected in asthmatic patients, up to 50% of patients were identified as suffering concomitant ILO and asthma.[6,7]

Both asthma and ILO may present with dyspnoea and wheezing upon exposure to certain triggers such as physical exertion or inhaled irritants, making differentiation between the two conditions a clinical challenge.[7] Due to the similarities in presentation, many people with underlying ILO are misdiagnosed with refractory asthma. A retrospective study estimated that it took an average of 4.8 years for a patient with misdiagnosed asthma to be correctly diagnosed with ILO.[8] Treatment for asthma in misdiagnosed patients with underlying ILO is of little benefit, and patients are therefore unnecessarily suffering significant morbidity and are subject to high doses of potentially toxic treatments such as systemic steroids.[7,9] Aside from patient morbidity the economic impact of ILO misdiagnosis and untargeted treatment is likely high,[10,11] although robust cost-analysis data is lacking. It is therefore vital that clinicians are able to competently distinguish the two conditions.

This study aimed to identify triggers for both ILO and asthma and compare the prevalence of each trigger between conditions, the outcome of which could assist clinicians in the diagnosis of ILO. In addition, the identification of disease-specific triggers may lead to novel hypotheses related to upper and lower airway hyper-responsiveness.

METHODS

Ethical approval was obtained from the Camden and Kings Cross Ethics Committee (16/LO/0911) and participants provided written informed consent.

Recruiting site

Participants were recruited from a specialist airway clinic at the Royal Preston Hospital. The physicians in the service were respiratory specialists with a sub-specialty interest in asthma. This is a tertiary level service, where patients (over the age of 16 years old) with breathlessness are referred from GP surgeries or hospital consultants. This multidisciplinary service provides a variety of physiological tests and treatments, including; laryngeal provocation, for the diagnosis of ILO, and bronchial provocation and bronchodilator reversibility tests, for the diagnosis of asthma. The standardised diagnostic work-up for ILO is presented in table 1. The diagnosis of asthma in the service would typically be based on previous pulmonary function tests and expert clinical assessment, with further testing only occurring in case of diagnostic difficulty. Comorbidities were self-reported and/or retrieved from patient's medical notes.

Retrospective case note review: Phase one

Data from consecutive patients with laryngoscopy-confirmed ILO between January 2015 and May 2016 attending the specialist airway clinic were included in the study. A retrospective case note review of patient's referral letters and medical notes was performed. Patient's demographics, comorbidities and triggers of breathlessness were identified and recorded. Triggers were then categorised under seven domains; scent, environment, mechanical, daily activities, emotions, temperature and others and used to inform the Breathlessness Trigger Survey.

Prospective questionnaire: Phase two

Participants

The prospective study was conducted over a short window (May to June 2016) in order to minimise any seasonal variability. Participants with endoscopically-proven ILO, and /or asthma were recruited from the specialist airways clinic. A participant information leaflet regarding the study was given to each eligible patient when they arrived at the clinic for their outpatient appointment. Study exclusion included i) no formal diagnosis of ILO or asthma and ii) other conditions that may cause breathlessness. Participants with both ILO and asthma were eligible to

take part in the study provided that they were able to differentiate between triggers of breathlessness for each condition.

Questionnaires

The Breathlessness Triggers Survey is a 23-item survey made specifically for this project and based on the findings from the first part of the study. It evaluates the likelihood of each item being a trigger for breathlessness in either ILO or asthma. Patients respond to each item using a five-point Likert scale (1= strongly agree, 2= agree, 3= neutral, 4= disagree, 5= strongly disagree). If a single participant had both asthma and ILO, the participant was asked to complete this survey twice (one for each condition). The design of the Breathlessness Triggers Survey is described in the phase one results section below.

To characterise the study population, participants were asked to complete the St. George's Respiratory Questionnaire (SRGQ)[12] and the Medical Research Council (MRC) Dyspnoea Scale.[13] Participants with ILO were also asked to complete the Vocal Cord Dysfunction Questionnaire[14] and patients with asthma the Asthma Control Questionnaire.[15]

Statistical Analysis

The responses for each question in the Breathlessness Triggers Survey were grouped into strongly agreed/agreed, neutral and disagreed/strongly disagreed. The item was considered a trigger if the participant indicated either strongly agreed or agreed. A chi-square test was performed for each trigger to compare the percentages of those who agreed/strongly agreed between the two conditions. If the chi-square test indicates more than 20% have an expected count of less than five, the Fisher's exact was used to compare the difference between the two conditions. All statistical analyses were performed using SPSS v26.0 (IBM Corp, Chicago, Ill).

RESULTS

Phase One

Participants

Data from 202 patients with ILO [73% female, mean (SD) age 53.1 (15.7) years] were included in the retrospective study (table 2). The most common comorbidities were gastro-oesophageal reflux

disease (GORD), asthma and mental health conditions such as depression and general anxiety disorder.

Number of Triggers for Breathlessness

The number of triggers indicated in patients' letters were recorded for each patient; the median (interquartile range) number of triggers per patient was 3 (3), with a maximum of 8. There was no mention of any triggers in the patients' notes for 18 patients.

Types of Triggers

Reported triggers for ILO are presented in table 3. Of note, the most common individual triggers for ILO-induced breathlessness were physical exertion (37.3%), deodorant/aftershave/perfume scents (36.3%), talking (23.0%), cleaning sprays/liquids (18.1%), changes in temperature (15.2%) and stress (14.2%).

Survey Design

The data collated from the retrospective study were used to design a survey to evaluate the potential triggers of breathlessness for phase two of the study. All the triggers listed in table 3 were included in the breathlessness triggers survey and grouped under six categories; scent, environment, mechanical factors, daily activities, emotions and temperature. Two additional triggers, vinegar and after-meals, were also included in the survey based on clinical experience. A free-text section entitled 'others', was included to allow participants to add other triggers of breathlessness which were not listed in the survey.

Phase Two

Participants

A total of 89 participants were recruited for this study; 38 participants with ILO only, 39 participants with asthma only and 12 participants with both ILO and asthma. Table 4 shows the demographics and relevant comorbidities of the participants for the prospective study.

Questionnaires

A worse quality of life total score was reported by participants with both asthma and ILO compared to participants who had a diagnosis of only one of the conditions (table 4, $p<0.05$). However, no such between group differences were noted on the MRC dyspnoea scale (table 4). Likewise, no difference was noted between participants with both ILO and asthma and individuals with only one condition using the VCDQ and the ACQ (table 4).

Breathlessness Triggers Survey

Number of Triggers: The number of triggers indicated as agree/strongly agree in the Breathlessness Triggers Survey were summed for each participant. The mean (SD) number of triggers in the asthma and ILO cohorts were 11 (6) and 13 (5) respectively, p=0.132.

Types of Triggers: The proportions of participants in each cohort reporting each trigger of breathlessness are presented in figure 1a-f and summarised below.

Smells: The majority of participants with ILO or asthma agreed that perfumes/deodorants (76% and 61% respectively) and cleaning sprays (74% and 63%) triggered their breathlessness with no difference in frequency between conditions ($p>0.05$). Although the majority of participants in both cohorts disagreed that vinegar would trigger their breathlessness, it was more likely to trigger breathlessness in patients with ILO compared to asthma (22% *versus* 6%, p=0.019) (figure 1a).

Environmental Factors: Smoke/fumes affected more than 80% of both cohorts without a between group difference in frequency ($p>0.05$), whereas damp and pollen/flowers were more problematic for the asthma group compared to those with ILO (71% *versus* 46%, p=0.012 and 78% *versus* 52%, p=0.005, respectively) (figure 1b).

Mechanical Factors: There was a significant difference between the ILO and asthma cohorts for three of the four mechanical triggers; talking (78% *versus* 41%, $p<0.001$), shouting (80% *versus* 55%, $p = 0.007$) and swallowing (66% *versus* 35%, $p =0.002$), but not laughing (68% versus 59%, respectively, p=0.339) (figure 1c).

Daily Activities: The majority of participants with ILO (72%) and asthma (78%) agreed that exercise was a trigger for their breathlessness, however there were no between-cohort differences in frequency (p=0.454, figure 1d).

Emotions: A large proportion of participants with ILO (86.0%) and asthma (73%) agreed that stress was a trigger of their breathlessness (p=0.096) (figure 1e).

Temperature: The majority of participants in both cohorts agreed that the extremes of temperatures could trigger their symptoms, especially cold air, with no difference between the two groups (figure 1f).

DISCUSSION

To our knowledge this is the first study to investigate self-reported triggers of breathlessness in both ILO and asthma. A 23-item Breathlessness Triggers Survey was designed through a retrospective case note review of referral letters and medical notes in 202 patients with

laryngoscopy-confirmed ILO. The triggers identified in the case review were confirmed in an independent sample of patients with ILO and compared to a sample of patients with asthma who completed the breathlessness triggers survey. Out of 23 suggested triggers in the survey, six showed a difference in prevalence between the two cohorts; three 'Mechanical Triggers' (talking, swallowing and shouting) were more prevalent in ILO, two 'Environmental Triggers' (pollen/flowers and damp environment) were more prevalent in asthma and one 'scent' (vinegar) was more prevalent in ILO. Exercise was a trigger for the majority of patients with asthma and/or ILO. Knowledge of the difference in prevalence of these triggers may aid clinicians in making swifter and more accurate diagnoses of ILO and may reduce the misdiagnosis of asthma in this population.

The most evident finding of this study was the significantly higher prevalence of mechanical factors such as talking, shouting and swallowing in triggering symptoms of breathlessness in ILO participants compared to patients with asthma (figure 1c). The high occurrence of mechanical triggers in ILO is in keeping with our understanding of the pathophysiology of the condition.[16] Indeed, neural hypersensitivity and/or mechanical insufficiency are proposed as key underlying mechanisms in ILO.[4] Laryngeal hypersensitivity is thought to be a consequence of underlying inflammation which could be caused by associated comorbidities such as GORD or post-nasal drip, or extrinsic irritants such as dust particles.[17,18] Chronic inflammation may modify neural pathways, altering the perceptions and response of higher centres to afferent signals, leaving the neural pathways in a perpetually hyper-excitable state. In the context of hyper-excitability, the mechanical movements in the laryngeal region during speech and/or swallowing may be sufficient to trigger local reflexes which produce paradoxical adduction of vocal folds during inspiration. This may be particularly apparent in patients with mechanical insufficiencies, e.g., malfunctioning laryngeal abductor muscles or laxity of ligaments or laryngeal cartilage.[4] As asthma involves bronchial hyper-reactivity and not extra-thoracic/laryngeal hyper-reactivity, mechanical factors would be less likely to trigger symptoms of breathlessness in asthmatic patients.

In contrast, environmental triggers of breathlessness such as pollen/flowers and damp weather were more prevalent in patients with asthma compared with ILO (figure 1b). The role of pollen/flowers in triggering atopic asthma is well-established in literature. The role of damp weather in triggering asthma symptoms is less certain, but could be mediated through increased

ozone, airborne particulate matter, or mould spores. Airway hyper-responsiveness is a hallmark feature of asthma. Therefore, the higher frequency of certain environmental triggers in asthma may be explained by the deposition of environmental irritants distal to the larynx, in the hyper-responsive large and/or small airways. Where environmental triggers were commonplace in both ILO and asthma (dry air and smoke/fumes), both proximal and distal hyper-reactivity is likely the explanation, however would not aid in the differentiation of the conditions.

The four-fold increase in prevalence of vinegar as a trigger in ILO patients may be useful to distinguish patients with ILO and patients with asthma. However, the diagnostic value may be limited as only 1 in 5 patients with ILO indicated vinegar as a trigger of their breathlessness. Vinegar is largely made up of acetic acid and water, with several other chemicals in low concentrations. The acidic nature of vinegar could potentially cause irritation to a hypersensitive laryngeal area. However, with no literature regarding the association of vinegar and ILO, such theories are speculative, and future research could possibly look at the association between vinegar and ILO for a more conclusive explanation.

Our findings are most relevant to primary care practitioners where the majority of asthma diagnoses occur. Given that asthma may be incorrectly diagnosed in up to one third of cases,[19] and where ILO is the underlying condition in the misdiagnosis, patients may experience years of unnecessary treatment and increased morbidity,[10,11] improving diagnosis in primary care is of the uttermost importance. In primary care where physiological testing is limited by time and resource, diagnoses are predominantly informed by clinical symptoms. Our data suggest that practitioners should consider triggers of breathlessness, and the frequency of triggers across clinical populations, to assist with their diagnoses. Specifically, if a patient reports mainly mechanical triggers and/or vinegar as a trigger of breathlessness, ILO should be considered as an alternative diagnosis to asthma and patients referred for additional physiological testing for confirmation. Additional information such as the locality of the symptoms (bronchial or thoracic/laryngeal) and underlying comorbidities may also aid with clinical decision making.

Patients reporting exercise-induced respiratory symptoms such as dyspnoea, wheeze, cough and chest-tightness is a commonly-encountered clinical scenario in primary care.[20] In the current study, the majority of patients with ILO and/or asthma reported exercise as a trigger for

breathlessness. ILO and asthma triggered by exercise are commonly referred to as exercise-induce laryngeal obstruction (EILO) and exercise-induced bronchoconstriction (EIB), respectively. Although the trigger 'exercise' and the reported symptoms are common to both disease types, further interrogation of the clinical presentation may help clinicians differentiate the diagnosis. For example: i) the onset of ILO usually occurs early during peak exercise, whereas EIB typically occurs shortly following the cessation of exercise; ii) symptoms regress within in a few minutes of ceasing exercise with EILO, whereas the resolution of symptoms can be up to 20-30 minutes with EIB; iii) EILO is often associated with inspiratory noises (stridor), whereas EIB typically causes expiratory wheeze; and iv) unlike EIB, inhaled beta-2 agonists are usually ineffective in for the treatment of EILO.[21] In addition, our patients were older than those typically found to have EILO [22] and a study targeting this younger age group may reach different conclusions. Further, exercise-induced breathlessness can be a symptom in asthma and ILO, but causes by factors not directly linked to laryngeal or bronchial airflow obstruction, such as obesity and/or deconditioning. We would therefore propose that primary care physicians explore exercise as a trigger for breathlessness in more detail to assist in the differentiation ILO and asthma. Where inhaled therapy is largely ineffective, patients should be referred for assessment of ILO as a possible cause of exertional dyspnoea.

The ILO cohort in this study showed a greater percentage of participants with comorbidities such as GORD and mental health conditions (depression, anxiety). It is proposed that the acidic contents from GORD damage the laryngeal mucosa. The prolonged inflammatory insults may increase laryngeal sensitivity resulting in hypersensitivity of the laryngeal region. Thus, GORD may be a contributing factor in the development of ILO as well as a trigger for breathlessness. The association of ILO with mental health conditions such as depression, anxiety and stress has been extensively discussed in literature.[23-26]

A strength of this study lies in the robust diagnostic work up for patients with ILO (table 1), providing confidence in the accuracy of the diagnosis. This approach however combines several different phenotypes of ILO (e.g., glottic/supraglottic, fast/slow onset and different inducers of ILO), which may manifest in different symptomology and self-reported triggers. Future studies would benefit from additional sub-group analysis of ILO patients, and in deed more formal provocation challenges, in particular using exercise rather than relying solely on symptom

reporting. Unlike ILO, the diagnosis of asthma was not well-standardised in the current study, and the criteria for asthma diagnosis was not recorded. It is possible that the diagnosis relied on previous pulmonary function tests and clinical expertise and not further verified by physiological tests at the time of this study. Further, the current treatment of patients with asthma, which may affect patients' reported triggers, was not considered here. Finally, comorbidities were self-reported and/or retrieved from patient's medical notes, and again, may not have been verified physiologically.

Several other limitations worthy of consideration include the timing of the study and the validity of the Breathlessness Triggers Survey. Indeed, the study was performed during spring / early summer (May and June 2016), which may result in a consequent over-representation of certain triggers such as pollen. The Breathlessness Triggers Survey that was used in this study is not a validated questionnaire and, due to the nature of the study design, the list of potential triggers should not be considered exhaustive. To rectify this short-coming, a section at the end of the survey was present to allow participants to fill in other triggers which were not listed.

In conclusion, this study has taken the first step to identify triggers of ILO that could help differentiate the condition from asthma. Mechanical factors (i.e. talking, shouting and swallowing) and vinegar scent are more commonly reported triggers in patients with ILO while environmental factors (i.e. pollen/flowers and damp air) are more commonly reported as triggers by asthmatic patients. Clinicians in primary care, where the majority of symptom based diagnoses, and misdiagnoses, of asthma occur, should consider the different presentation of triggers when making a diagnosis.

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Table 1: Provocation laryngoscopy assessment protocol for inducible laryngeal obstruction

Baseline assessment	
Nasal examination	Note any abnormal anatomical, pathological, physiological presentations (e.g. septal deviations, nasal polyps, mucous secretions)
Oropharyngeal examination	Note any abnormal anatomical, pathological, physiological presentations (e.g. candida, velopharyngeal incompetency, mucous secretions)
Laryngeal examination	i) Observe the larynx at rest: • Note any structural abnormality, laryngopharyngeal reflux, pathology, mucous secretions, candida infection, inappropriate laryngopharyngeal constriction, asymmetry. • Note laryngeal movements during tidal breathing: ii) Observe the larynx during phonation (direct patient to say 'EE') • Note any constriction patterns, abduction/adduction abnormalities
Provocation Protocol	
Direct patient to: 1. Breathe deeply 2. Sniff and say EEE (repeat) 3. Count to 10 4. Count to 10 loudly and rapidly 5. Count to 10 with increasing volume (loudest at 10) 6. Breathe in and out rapidly through open mouth	Note any changes in laryngeal features during respiration as follows: I. Inducer (e.g. deep breaths, direct challenge) II. Location of obstruction; glottis, supraglottic, both III. Phase of respiratory cycle; inspiratory, expiratory, both IV. Onset of obstruction; fast (one breath to next)

7. Direct challenge (patient specific, e.g. odour exposure)
8. Symptom imitation

slow (over several breaths)

V. Resolution of obstruction;
fast (<5 minutes)
slow (> 5 minutes)

Table 2: Demographics of ILO participants for retrospective study

	n=202
Gender F:M (% Female)	148:54 (73)
Age (SD) yrs	53 (16)
Comorbidities (%)	
GORD	39
Asthma	39
Depression, anxiety	18
Other allergic diseases	11
Post-nasal drip	6

Table 3: Percentages of triggers of ILO retrieved from the records of patients included in the retrospective study.

Variable	% (n=202)
Smell	**43**
Deodorant, aftershave, perfume	36
Cleaning spray/liquid	18
Food scent	3
Nail varnish or nail varnish remover	1
Chilli pepper	1
Environmental Factors	**10**
Smoke	7
Dust	4
Dry	2
Damp	1
Pollen/Flowers	1
Temperature	**25**
Changes in temperature	15
Cold	13
Hot	2
Emotions	**17**
Stress	14
Anxiety	4
Excitable	1
General emotions	4
Mechanical Factors	**34**
Talking	23
Shouting, projecting voice	9
Laughing	11
Swallowing	5
Daily Activities	**41**
Physical exertion – walking, exercise, bending	37

During meals	3
Lying down flat	2
Others	**17**
Not indicated in letters	9
Patient unable to identify any triggers	8

Table 4: Participant characteristics for the prospective phase of the study.

	ILO (n=38)	**Asthma (n=39)**	**ILO and Asthma (n=12)**
Gender F:M (% Female)	24:14 (63)	22:17 (56)	10:2 (83)
Age	57 (16)	53 (13)	57 (14)
Comorbidities n (%)			
GORD	17 (45) *	8 (21)	3 (25)
Depression, anxiety	4 (11)	1 (3)	4 (33)*
Other allergic diseases	3 (8)	6 (16)	2 (17)
SGRQ mean (SD)			
Symptoms Score	46 (26)	66 (23)	74 (22)
Activity Score	57 (31)	64 (26)	78 (26)
Impact Score	40 (27)	42 (25)	49 (22)
Total Score	44 (24)	52 (23)	63 (20)*
MRC Dyspnoea Scale mean (SD)			
	3 (1)	3 (1)	4 (1)
VCDQ mean (SD)			
	46 (9)	-	47 (7)
ACQ mean (SD)			
	-	3 (1)	3 (1)

Mean (SD) scores of the St. George's Respiratory Questionnaire (SGRQ), Vocal Cord Dysfunction Questionnaire (VCDQ), Asthma Control Questionnaire (ACQ) and Medical Research Council (MRC) Dyspnoea Scale of participants from the prospective study. * $p < 0.05$

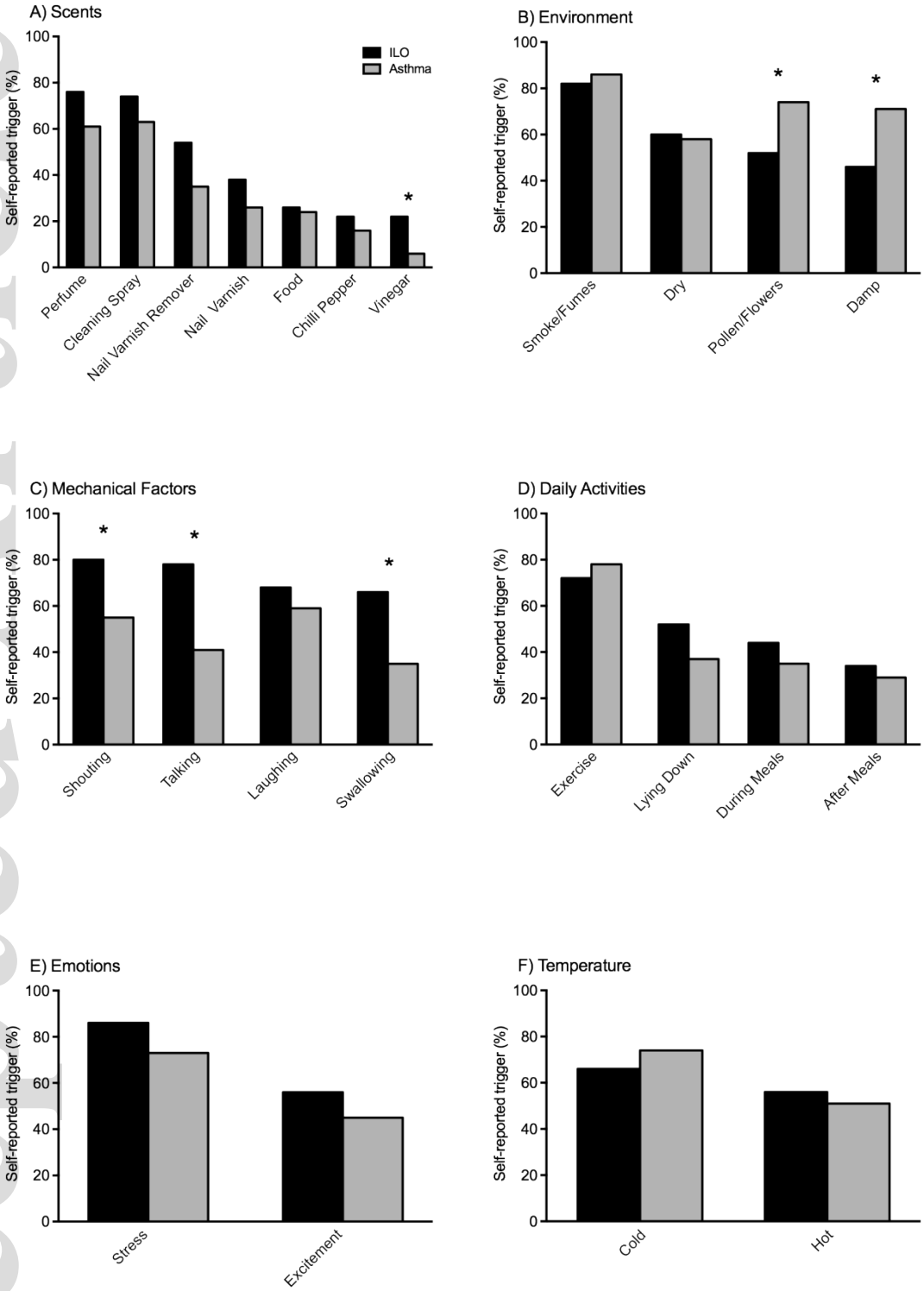

Figure 1(A)-(F): Self-reported triggers of breathlessness in patients responding to the Breathlessness Triggers Questionnaire in a prospective study of 89 patients with ILO and/or asthma. The triggers have been categorised into (A) scents, (B) environmental, (C) mechanical factors, (D) daily activities, (E) emotions and (F) temperature. * different between asthma and ILO at $p < 0.05$.