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Prevalence and impact of comorbid laryngeal dysfunction in asthma: A systematic review and meta-analysis

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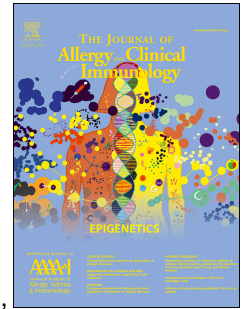
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TITLE PAGE**Prevalence and impact of comorbid laryngeal dysfunction in asthma: A systematic review and meta-analysis**

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Abstract

Background: Laryngeal or vocal cord dysfunction has long been regarded as a mimic of asthma; however recent evidence indicates that it may be a significant comorbid condition in asthmatics.

Objective: We aimed to systematically estimate the prevalence of comorbid laryngeal dysfunction (LD) in asthmatic adults and to characterize its clinical impact on asthma.

Methods: Electronic databases were searched for relevant studies published until June 2019. Studies were included if LD was objectively defined by direct visualization of laryngeal movement. Outcomes included the prevalence of LD and its association with clinical asthma indicators, such as severity, control and quality of life. Random effects meta-analyses were performed to calculate the estimates.

Results: A total of 21 studies involving 1,637 patients were identified. Overall, the pooled prevalence of LD in asthmatic adults was 25% (95% CI: 15-37%; $I^2=96\%$). Prevalence estimates differed according to the diagnostic test utilized with lowest overall prevalence (4%; 95% CI: 0-10%; $I^2=90\%$) seen when LD was diagnosed by resting laryngoscopy without external stimuli; however, it was much higher in laryngoscopy studies utilizing external trigger, such as exercise (38%, 95% CI: 24-53; $I^2=90\%$) or in those using a CT-based diagnostic protocol (36%; 95% CI: 24-49; $I^2=78\%$). Only seven studies reported the associations between LD and clinical asthma indicators; inconsistencies between studies limited meaningful conclusions.

Conclusion: LD may be a common comorbidity in asthma, affecting about 25% of adult patients. Further prospective studies are needed to better characterize its clinical impact and benefits of detecting and managing LD in asthmatic patients.

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Capsule summary

This systematic review reveals that laryngeal dysfunction is present as a comorbid phenomenon in approximately one in four adult asthmatics, highlighting that clinicians should consider this section of the airways when assessing asthma.

Clinical implications

Laryngeal dysfunction may be a common comorbid condition in adult asthma. Further investigation is warranted to better characterize the clinical impact of detecting and treating laryngeal dysfunction in asthmatic patients.

Key words: laryngeal dysfunction, vocal cord dysfunction, inducible laryngeal obstruction, asthma, treatable traits, prevalence, systematic review

68 **Abbreviations**

69 LD, laryngeal dysfunction

70 VCD, vocal cord dysfunction

71 ILO, inducible laryngeal obstruction

72 CT, computed tomography

73 95% CI, 95% confidence interval

INTRODUCTION

The presence of comorbid upper airway disease in individuals with asthma is recognized to have a deleterious impact on symptom assessment and disease control.¹ In this context, it is now widely acknowledged that the detection and treatment of comorbid nasal disease is key in optimizing asthma management.² It has, however, more recently become apparent that the assessment and evaluation of dysfunction in other segments of the airway tract is also relevant when optimizing asthma care.^{3, 4} Specifically, the co-existence of laryngeal dysfunction (LD) may act to not only mimic asthma, but also present as a comorbid phenomenon; acting to amplify symptoms, impair exercise tolerance, and increase treatment burden.⁵⁻⁹

The larynx, as the anatomical ‘gatekeeper’ of the airways is required to simultaneously reconcile several functions including phonation, swallowing, and airway protection. It is one of the most highly innervated structures in humans, with an elaborate neural network, triggering immediate closure on exposure to external stimuli.¹⁰ In a proportion of individuals, the behavior of the larynx may appear to be altered to what could be considered to be a maladaptive or dysfunctional pattern. In this state, the laryngeal inlet can close inappropriately (i.e. in response to non-harmful stimuli such as scents, exercise or environmental conditions) or excessively, causing profound breathlessness, stridor and in some cases even syncope.¹⁰ This aberrant laryngeal response or dysfunction is described in the literature using several different terms, including laryngospasm, vocal cord dysfunction (VCD), or paradoxical vocal fold movement. More recently, inducible laryngeal obstruction (ILO) or LD have been proposed as umbrella terms to encompass the wide variety of aberrant laryngeal response patterns.¹⁰⁻¹³

To date, there is a paucity of studies in the literature that have systematically and

comprehensively evaluated the epidemiology of LD as a comorbid phenomenon in asthmatics. Individual studies have however highlighted the potential importance of LD with prevalence estimates of up to 75% of individuals with asthma.^{6, 8, 9, 14-16} Differences in study design and population characteristics have however confounded a true understanding and appreciation of the relevance of comorbid LD in this context.

The aim of this study is, therefore, to systematically review the prevalence of comorbid LD and characterize its relevance to standard clinical control and outcomes measures in adults with asthma. To improve precision in this context, we only included studies that defined LD on the basis of objective methodology; i.e. with visualization of excessive or inappropriate glottic behavior, using either a laryngoscopic or computed tomography (CT)-based diagnostic approach, in patients diagnosed with asthma. In this study, we used LD to encompass various terms for the condition with an aberrant laryngeal response, including VCD and ILO.^{11, 12}

Methods

Search strategy and selection criteria

We conducted a systematic literature search to identify studies that had relevant information to address the following research questions:

- Question 1: What is the prevalence of LD in adult patients with asthma?
- Question 2: Does comorbid LD impact on clinical asthma disease markers, such as asthma severity, control and quality of life?

We performed a systematic search of PubMed, Embase, and Cochrane Library databases for articles published in peer-reviewed journals up to June 2019. The search strategy is summarized in Supplementary Table S1 in the Online Supplement. Briefly, search terms included keywords for asthma and LD and its differential diagnoses including VCD, ILO, laryngospasm, or paradoxical vocal fold movement.¹² Language was not restricted. The review process followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁷ The study protocol was registered in PROSPERO (registration number CRD42019119820).

Studies were included if they met the following criteria: studies which 1) specified the diagnostic criteria of asthma employed, 2) objectively defined LD by direct visualization of laryngeal movement, and 3) reported the prevalence or clinical relevance of LD. With regards to age criteria, studies covering a broad range of age groups were included if they were mostly adults. Studies were excluded if: 1) the diagnosis of LD was only based on spirometry, questionnaires, or clinical symptoms, without visualization of the larynx, 2) the population was not relevant to asthma, 3) the population was limited to children only, 4) the prevalence of LD or its association with asthma outcomes was not reported, 5) there were no original data, or 6) they were duplicates. We included conference abstracts if they reported

sufficient information. Any discrepancy was resolved by discussion between the main authors.

Data extraction

From all the included articles, we extracted the following outcomes: study design, region, publication year, population characteristics, diagnostic criteria of asthma, asthma activity outcomes (severity, control status, or asthma-specific quality of life), and diagnostic criteria and prevalence of LD. If the outcomes were not originally described but were deemed potentially available from the original dataset, we contacted the corresponding authors via email.

Quality assessment

There is no widely accepted tool for assessing the quality of patient-based prevalence studies. Therefore, we chose and modified items regarding external and internal validity from the assessment tools for population-based prevalence studies¹⁸ and diagnostic studies¹⁹, which included sample size justification ('Was a consecutive or random sample of patients enrolled?'), appropriate selection criteria ('Did the study avoid inclusion and exclusion criteria that could potentially bias toward the presence or absence of LD?'), case definition ('Was an objective case [asthma] definition used in the study?'), and outcome definition ('Was the study instrument that measured the parameter of interest [LD] sufficiently specific?'). Discrepancies in data extraction and quality assessment were resolved by discussion between the main authors.

Statistical analysis

The pooled prevalence of LD was estimated using random-effects meta-analyses to account

for potential clinical and methodological heterogeneities in observational studies. As the prevalence of LD may vary between diagnostic methods (e.g., either with or without external stimulation, or either laryngoscope or larynx CT), subgroup analysis was undertaken as per the diagnostic approach used. Further subgroup analyses were also planned according to the definition of asthma and patient characteristics. Heterogeneity was first assessed using a visual forest plot inspection and I^2 statistics. Sensitivity analyses were considered to further explore the heterogeneity according to study characteristics. We used funnel plot asymmetry and Egger's tests to assess publication bias when appropriate.²⁰ All statistical tests were two-tailed, and a p -value < 0.05 was considered to be statistically significant. All meta-analyses were conducted using software MetaXL 5.3 (EpiGear International Pty Ltd) and the meta-analysis module of Stata (version 15.1; StataCorp, College Station, Tex; metabias).

Results

From the 6,085 studies initially retrieved publications, a total of 21 studies comprising 1,637 participants were finally selected. A flow chart outlining the selection process and detailed identification is presented in Figure 1. Eighteen studies^{6, 7, 9, 14, 21-34} were full papers, and three studies³⁵⁻³⁷ were conference abstracts. Sixteen studies^{9, 14, 21-31, 35-37} defined LD using endoscopy (either laryngoscopy or bronchoscopy), whereas five studies utilized a CT-based approach.^{6, 7, 32-34}

Baseline characteristics of the 21 included studies are summarized in Tables 1-2 and in Supplementary Table S2 in the Online Supplement, grouped by diagnostic methods. Study design and quality assessment for each study is summarized in the Online Supplement and Supplementary Table S3. All but two of the endoscopic studies^{14, 23} were of prospective design. The number of study participants ranged from 15 to 354. The definitions of asthma used in each study are summarized in Supplementary Table S2 in the Online Supplement.

Laryngoscopy-based assessment

Laryngoscopy-based studies were sub-grouped by the use of an external trigger or provocation agent to provoke or stimulate LD; accordingly ten studies^{9, 14, 26-31, 36, 37} included provocation maneuvers using external stimuli, whilst six studies^{21-25, 35} did not. Exercise was the most frequent stimulus employed; other stimuli included deep breathing, phonating, panting, sniffing, and chemical exposure. Amongst the six laryngoscopic studies that did not utilize an external triggers, one study²⁵ defined asthma based on objective evidence of variable airway obstruction, whereas five others were based physician-diagnosed asthma according to international guideline criteria.^{21-24, 35} Among the ten laryngoscopic studies using external triggers, seven studies^{9, 26-28, 30, 31, 36} utilized objective spirometric evidence to define

asthma, showing reversible airflow obstruction, airway hyperresponsiveness, or variable lung function over time. Three others relied on physician-diagnosed asthma according to the internationally accepted guideline criteria.^{14, 29, 37}

Computer tomography-based assessment

Five prospective studies^{6, 7, 32-34} describe the prevalence of LD utilizing a specifically configured CT protocol (320 slice-based methodology), based on comparison with a control population, to detect inappropriate or excessive laryngeal closure. In these studies, the number of study subjects ranged from nine to 155. Three studies^{6, 7, 32} recruited asthmatic patients from a tertiary severe asthma outpatient clinic, whereas one multi-center study³³ recruited patients from general practice or hospital asthma clinics using the International Study of Asthma and Allergies in Childhood survey criteria for asthma diagnosis.³⁸ One other study³⁴ consecutively recruited patients during an exacerbation of symptoms (requiring hospitalization) from an emergency department. All CT studies were performed without the use of an external trigger stimuli and in the supine position, necessitated for axial imaging.

Prevalence of comorbid laryngeal dysfunction in asthmatics

Overall, the pooled prevalence of LD among asthmatics was 25% (95% confidence interval [95% CI]: 15-37%; $I^2=96\%$), ranging from 0 to 75% (Figure 2). The prevalence differed based on the diagnostic test applied; subgroup analyses revealed the prevalence to be as low as 4% (95% CI: 0-10%; $I^2=90\%$) in the six endoscopic studies that did not employ an external trigger,^{21-25, 35} but was much higher (38% [95% CI: 24-53%; $I^2=90\%$]) in studies that employed an external trigger stimuli when measuring laryngeal movement,^{9, 14, 26-31, 36, 37} and was equally high in larynx CT studies as 36% (95% CI: 24-49%; $I^2=78\%$).^{6, 7, 32-34} A funnel

plot was examined in ten endoscopic studies with external stimuli, suggesting publication bias was not likely (Supplementary Figure S1 in the Online Supplement). The prevalence of comorbid LD among non-asthmatic controls was examined in two studies identified in this review, and was found to be significantly less frequent than asthmatics (5% vs. 0%²² and 19.1% vs. 5%²⁷, respectively).

Subgroup analyses were performed to evaluate sources of heterogeneity in the prevalence estimates between studies. The possible effect of different asthma definitions (objectively diagnosed [based on reversible airway obstruction or hyper-responsiveness] vs. physician-diagnosed asthma) was examined through subgroup analyses of the ten endoscopic studies employing external triggers. Although the heterogeneity was large and the number of included studies per subgroup was small, the pooled prevalence did not greatly differ based on asthma definition employed (in 7 studies of objectively diagnosed asthmatics^{9, 26-28, 30, 31, 36}, 36% [95% CI: 22-51%; $I^2=83\%$]; and in 3 studies of physician-diagnosed asthmatics^{14, 29, 37}, 42% [95% CI: 5-84%; $I^2=96\%$]) (Figure 3A). The prevalence did differ based on the patient characteristics (Figure 3B); the two studies that recruited patients referred with suspicion of LD^{14, 31} revealed a much higher prevalence of the condition (71% [95% CI: 62-79%; $I^2=0\%$]) than others, although they did not specify the key indicators driving the initial clinical suspicion of LD. In studies specifically addressing exertional dyspnea, four studies of asthmatic patients^{9, 28, 30, 39} found a much lower prevalence (36% [95% CI: 24-49%; $I^2=38\%$]) than the former two studies of patients with suspected LD^{14, 31} but a higher prevalence than other studies of patients not selected for exertional dyspnea (Figure 3B).^{26, 27, 29}

In sensitivity analyses, it was found that retrospective study design, lack of patient exclusion criteria, or less specific diagnostic criteria for LD might be a further source of heterogeneity in the prevalence estimates (Supplementary Table S4 in the Online

Supplement).

Nine studies^{6, 9, 14, 24, 28, 29, 32-34} provided comparative information on demographics between asthmatics with and without LD. The proportion of females among asthmatics with and without LD and was 76 % (95% CI: 69-83%) and 74% (95% CI: 62-84%), respectively (Supplementary Figure S2 in the Online Supplement).

Associations of comorbid laryngeal dysfunction with asthma outcomes

Only seven studies^{6, 9, 14, 27, 28, 33, 34} reported any association between comorbid LD and asthma outcomes, such as asthma severity or control status (Supplementary Table S5 in the Online Supplement), and moreover, none of these studies were prospectively designed to test these associations. Meta-analysis could not be performed here due to a lack of commonality in assessment measurements. Six studies^{6, 14, 27, 28, 33, 34} examined the relationship between asthma severity (of different classifications) and LD; one study¹⁴ found a slightly higher prevalence of LD in severe asthmatics (intermittent, 41.7%; mild persistent, 75%; moderate persistent, 86.4%; severe persistent, 84.6%, $p=0.03$). However, it should be noted that in the retrospective study¹⁴ there was a very high overall prevalence of VCD (44/59, 74.6%) and that most patients with comorbid LD (33/44, 75%) had mild to moderate asthma. Other studies^{6, 27, 28, 33, 34} did not report any significant association with asthma severity.

Five studies^{6, 9, 14, 28, 33} compared asthma control status according to the presence of LD. Parsons et al.¹⁴ reported poorer asthma control, as measured by the Asthma Therapy Assessment Questionnaire, in asthmatics with comorbid LD. In the study by Low et al.³³, the proportion of patients with asthma control questionnaire-5 scores > 1.5 was significantly higher in asthmatics with LD than those without (13/26 vs. 13/65, $p=0.01$), but the proportion of patients with asthma control test scores < 16 did not differ according to the presence of LD

(12/26 vs. 29/65, $p=0.81$). Three other studies^{6, 9, 28} did not find significant difference in asthma control outcomes between those with and without LD.

Potential impact on specific symptoms of asthma is reported in 7 studies (Supplementary Table S6 in the Online Supplement).^{14, 25, 27, 29-31, 33} The symptom measurement scales were not standardized in most components and thus the results could not be pooled. However, there was evidence of a trend towards more stridor or choking in asthmatics with LD than in those without.

Discussion

The present systematic review and meta-analyses demonstrate that LD is a common comorbidity in adult asthmatics, affecting approximately one in four patients. Indeed, the prevalence increases to about one in three when assessment is undertaken using laryngoscopy with application of an external trigger or provocation methodology which is accepted to be the gold standard means for the diagnosis of LD.^{6, 10} These high prevalence estimates remained consistent in subgroup analyses of studies based on differing asthma diagnostic criteria and overall strongly indicate the need for clinicians to consider this comorbidity in the asthmatic population and also to assess potential clinical impact of LD.

As our systematic review focused only on asthmatic populations, it may be questioned whether the presence of LD is truly abnormal. However, two studies identified in this systematic review^{22, 27} compared the prevalence of LD between asthmatics and matched controls, and found that LD is significantly more frequent in asthmatics. This supposition is supported by general population studies indicating the prevalence of exercise-induced laryngeal obstruction approximates 5-7%.^{40, 41}

Our analysis revealed a difference in the prevalence of LD according to the type of methodology employed with external trigger application revealing a higher prevalence of LD. The best methodological approach to diagnosis of LD remains to be determined and there are advocates of both a laryngoscopy-based approach and imaging-based techniques. Moreover, others have argued that a true diagnosis is dependent on the presence of simultaneous symptoms and evidence of change in airflow parameters.¹² Certainly simple laryngoscopy provides only a snapshot of laryngeal behavior and in many cases may remain entirely normal at the time of assessment, in an individual who is well. In contrast, challenge laryngoscopy (using external triggers such as exercise or other environmental triggers) are

considered to be more valid, although there is still no accepted international consensus guidance on how to perform the challenge testing or exposure protocol.¹⁰ Recently, Hull et al. have described a continuous laryngoscopy during provocation protocol,⁴² but the degree of exposure and outcome measures are yet to be agreed.

A secondary aim of our work was to explore the impact of LD on clinical outcomes in asthma, assessing measures such as those addressing asthma severity and control. Unfortunately, it was impossible to draw a firm conclusion in the present review, because the number of reports and the sample size was small, and the outcomes utilized were not uniform across studies. Further studies are thus warranted with sufficient power to examine this association.

Clinically, LD appeared in some studies to be more prevalent in those with more severe disease and as might be expected in patients reporting exertional dyspnea, stridor, or choking (Figure 3B and Table S6 in the Online Supplement); thus, it is also hypothesized that LD is more relevant to a subset of patients with certain clinical features or phenotype, such as hypersensitivity to environmental triggers.

It is beyond the scope of the present systematic review to address the clinical benefits of management of LD, but it has been recently highlighted that LD should be considered a treatable trait in chronic airway disorders.^{3, 4, 43} Injection of botulinum toxin or speech language pathology therapy improved asthma outcomes such as asthma control test or medication scores in asthmatics with LD and an multidisciplinary team-based approach to the assessment and management of LD appears to be effective.^{7, 44-46} Moreover, in patients with chronic refractory cough and LD, speech pathology therapy was shown to be effective in controlling cough.⁴⁷ Patients with LD are often the recipients of a significant treatment burden, including maintained or frequent course of oral corticosteroids.^{15, 48, 49} Moreover,

there is an overlap in clinical presentation during acute exacerbation,³⁴ confounding correct treatment selection. Repeated exposure to systemic corticosteroids is known to increase future risk of complications such as diabetes mellitus, osteoporosis or fracture.⁵⁰ Thus, precise identification and control of LD will improve long-term health outcomes in these patients.

Several limitations should be considered in the interpretation of our findings. Firstly, the number of included studies and patients was small, despite the use of a rigorous literature search. Moreover, almost all studies included were conducted at single centers, which may limit the generalizability of our findings. There is a need for more broadly reaching collaborative work and improved consensus with respect to the best diagnostic approach. Secondly, there was a considerable heterogeneity in study design, outcome definition and the prevalence estimates. We conducted subgroup and sensitivity analyses to explore potential source of heterogeneity, but the heterogeneity could not be fully investigated because of the limited number of studies included. Thirdly, as all the included studies had cross-sectional design, a causal effect or relationship could not be assessed or assumed. Finally, publication bias could not be fully determined due to the limited number of included studies in some diagnostic test subgroups. However, we tried to minimize publication bias by searching for non-English literature and conference abstracts. Despite the limitations, our study has unique strength in that it is the first systematic review on the prevalence and clinical impact of LD in asthmatics. It also identified knowledge gaps in our understanding of LD in the context of asthma.

Certainly, our findings underpin the need for further prospective multi-center studies. However, such studies are inherently difficult to plan and conduct in part due to a lack of accepted 'gold-standard' diagnostic criteria. It is promising to see the development of

objective assessment systems to characterize laryngeal movement^{6, 51} and validated outcome measures.⁵² It is also a priority to utilize provocation protocols that are reliable and precise in detecting LD, but it will be important to assess the validity of this type of methodology.

In conclusion, the present systematic review and meta-analysis suggests that LD is a common comorbidity in adults with asthma. Further studies are now needed to better characterize the impact of comorbid LD in asthma and to investigate potential clinical benefits of detecting and managing LD in asthmatic patients.

Contributors

WJS and JH conceived the idea for this study. JHL and WJS conducted the literature search, data extraction, and statistical analyses. JHL, WJS, and JH wrote the first version of the manuscript and all authors revised and approved the final manuscript.

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Figure Legends

Figure 1. Flowchart of the search strategy and study selection

Figure 2. Forest plot of prevalence of laryngeal dysfunction in asthmatics

Figure 3. Subgroup analyses of prevalence of laryngeal dysfunction according to (A) asthma definitions utilized and (B) patient characteristics in 10 endoscopic studies utilizing external triggers

Table 1. Summary of endoscopic studies to define laryngeal dysfunction in adult patients with asthma

Study	Study design	Study subjects (age, yrs)	Diagnosis of laryngeal dysfunction				
			Diagnostic tool	Diagnostic criteria	Stimulation	Respiratory cycle	Prevalence (%)
Endoscopic studies without stimulation							
Jain et al. 2006 ²¹	Prospective	48 adults with acute asthma exacerbation (age range: 17-50)	Videolaryngoscopy	Anterior two-thirds closure of the vocal cords with formation of a posterior diamond-shaped opening	None	During inspiration and expiration	5/48 (10.4)
Dogan et al. 2007 ²²	Prospective	40 patients with mild-to-moderate asthma (mean age: 39.95) 40 age- and gender-matched non-asthmatic controls	Videolaryngoscopy	Abnormality of at least one parameter: pattern of glottic closure, degree of glottic closure, periodicity, amplitude, symmetry, mucosal wave, non-vibratory segments and adduction of ventricular bands	None	ND	2/40 (5) in asthmatics 0/40 (0) in non-asthmatic controls
Bisaccioni et al. 2009 ²³	Retrospective	245 adults with severe persistent asthma (age range: 21-85)	Videolaryngoscopy	Two-thirds closure of the vocal cords with a diamond-shaped opening occurring posteriorly	None	During inspiration	4/245 (1.6)
Oktay et al. 2009 ²⁴	Prospective	35 adults with acute asthma attack (mean age: 44.5)	Videolaryngoscopy	Abnormal vocal cord function	None	ND	0/35 (0)
Chan et al. 2015 ³⁵	Prospective	354 patients with severe asthma (age: no information)	Broncho- and nasoendoscopy	Paradoxical vocal cord movement	None	During inspiration and expiration	3/354 (0.8)
Denton et al. 2018 ²⁵	Prospective	157 patients with difficult-to-treat asthma (mean age: 52)	Laryngoscopy	Paroxysmal vocal fold motion	None	ND	25/157 (15.9)
Endoscopic studies with stimulation							
Hira et al. 2009 ²⁶	Prospective	35 patients with refractory asthma (age range: ≥12)	Bronchoscopy	Abnormal adduction of vocal cords	Speech, panting, sniffing, and deep breathing maneuvers	During inspiration and expiration	9/35 (25.7)
Yelken et al. 2009 ²⁷	Prospective	94 adults with asthma (age range: 21-72) 40 controls without any laryngological and respiratory diseases	Laryngoscopy	Adduction of the anterior two-thirds of the vocal cords and a posterior chinking or diamond-shaped glottic gap	Simulation of asthma attacks → (if normal) light physical exercise, repetitive, rapid deep inspirations, panting, sniffing, coughing, throat clearing; alternatively, phonating the /i/ vowel and other speaking tasks conducted rapidly and loudly	During inspiration and expiration	18/94 (19.1) in asthmatics 2/40 (5) in controls
Christensen et al. 2010 ³⁶	Prospective	22 patients with continued asthma symptoms despite treatment among a cohort of elite athletes with suspected asthma (age range: 12-35)	Continuous laryngoscopy during exercise testing	Abnormality assessed with a diagnostic measuring tool (EILOMEA software) ³⁹	Exercise	During inspiration and expiration	10/22 (45.5)

Parsons et al. 2010 ¹⁴	Retrospective	59 patients with mild-to-moderate asthma referred for videolaryngostroboscopy (mean age: 43.6)	Videolaryngoscopy	Inappropriate vocal cord constriction during the respiratory cycle and normal complete abduction during some portion of the exam	Sustained vowel production during oral and nasal breathing → (if normal) challenge with exercise → (if still normal) chemical challenge using perfumes or nontoxic cleaning solutions	During inspiration and expiration	44/59 (74.6)
Taverne et al. 2014 ²⁸	Prospective	15 patients with uncontrolled asthma and unexplained exertional dyspnea (mean age: 48.5)	Endoscopy during bicycle exercising	Progressive decrease of vocal cord opening angle compared to control group	Exercise	During inspiration	4/15 (26.7)
Porsbjerg et al. 2015 ³⁷	Prospective	28 patients with asthma (age: no information)	Continuous laryngoscopy during exercise testing	Norwegian grade score of ≥ 2 (at least moderate) ⁵³ for either glottic or supraglottic obstruction	Exercise	During inspiration and expiration	11/28 (39.8)
Pinto et al. 2016 ²⁹	Prospective	80 patients with severe asthma (median age: 49.5)	Nasal laryngoscopy	Paradoxical movements caused by vocal cord adduction	Forced respiration	During inspiration	14/80 (17.5)
Walsted et al. 2017 ³⁰	Prospective	23 patients with asthma and exercise-related symptoms among subjects with possible asthma and exercise-related symptoms but without suspicion of EILO or VCD (age range: 15-45)	Continuous laryngoscopy during exercise testing	Norwegian grade score of ≥ 2 (at least moderate) ⁵³ for either glottic or supraglottic obstruction	Exercise	During inspiration and expiration	5/23 (21.7)
Lee et al. 2018 ³¹	Prospective	44 adults with asthma among 69 consecutive patients with suspected co-existing ILO (age range: 18-72)	Flexible laryngoscopy	Vocal cord adduction during inspiration, or >50% vocal cord adduction on expiration	Mannitol	During inspiration and expiration	29/44 (65.9)
Hull et al. 2019 ⁹	Prospective	32 patients with severe asthma and persistent exertional dyspnea (mean age: 44)	Continuous laryngoscopy during exercise testing	Abnormal laryngeal closure at rest or near-maximal exercise (closure score ≥ 2) ⁵³	Exercise	During inspiration and expiration	15/32 (46.9)

ILO, inducible laryngeal obstruction; EILO, exercise-induced laryngeal obstruction; VCD, vocal cord dysfunction; ND, not described

Table 2. Summary of larynx computed tomography studies to define laryngeal dysfunction in adult patients with asthma

Study	Study design	Study subjects (age, yrs)	Diagnosis of laryngeal dysfunction				
			Diagnostic tool	Diagnostic criteria	Stimulation	Respiratory cycle	Prevalence (%)
Larynx CT studies							
Holmes et al. 2009 ³²	Prospective	9 adults with severe asthma and suspected VCD (age range: 30-75)	320-slice CT larynx	1) Vocal cord narrowing on expiration (compared with inspiration) clearly exceeded 40% 2) Any narrowing of the vocal cords also had to be sustained for >70% of either gated inspiration or expiration time to exclude transient changes that may reflect normal vocal cord movement	None	During inspiration and expiration	4/9 (44.4)
Low et al. 2011 ⁶	Prospective	46 patients with difficult-to-treat asthma and chronic or episodic severe breathlessness (mean age: 54.7)	320-slice CT larynx	Abnormal vocal cord movement was defined as below the predefined lower limit of normal (1.5 SD below the predicted mean)	None	During inspiration and expiration	23/46 (50)
Baxter et al. 2014 ⁷	Prospective	82 patients with refractory asthma who remained severely symptomatic	320-slice CT larynx	Abnormal vocal cord movement was defined as below the predefined lower limit of normal (1.5 SD below the predicted mean)	None	During inspiration and expiration	38/82 (46.3)
Low et al. 2017 ³³	Prospective	155 patients with asthmatics (mean age: 53.6)	320-slice CT larynx	Abnormal vocal cord movement was defined as below the predefined lower limit of normal (1.5 SD below the predicted mean)	None	During inspiration and expiration	57/155 (36.8)
Daley et al. 2019 ³⁴	Prospective	34 adults with acute asthma exacerbation who required hospital admission (mean age: 42.2)	320-slice CT larynx	Abnormal vocal cord movement was defined as below the predefined lower limit of normal (1.5 SD below the predicted mean).	None	During inspiration and expiration	6/34 (17.6)

CT, computed tomography; VCD, vocal cord dysfunction; SD, standard deviation

Table 3. Sensitivity analyses of 8 endoscopic studies with stimulation (excluding 2 studies of patients recruited with suspicion of laryngeal dysfunction^{14, 31})

Parameter	Number of studies	Prevalence of laryngeal dysfunction (95% CI)	I ² (%)
Asthma diagnosis			
Physician diagnosed asthma	2 ^{29, 37}	0.258 (0.070-0.500)	80
Asthma diagnosis based on bronchodilator response or airway hyper-responsiveness	6 ^{9, 26-28, 30, 36}	0.300 (0.203-0.408)	59
Patient selection criteria			
Patients with exertional dyspnea	4 ^{9, 28, 30, 36}	0.363 (0.241-0.493)	38
Patients with refractory or poorly controlled asthma (irrespective of exertional symptoms)	2 ^{26, 29}	0.202 (0.131-0.282)	4
Unselected recruitment	1 ²⁷	0.192 (0.118-0.278)	
Insufficient information (abstract only study)	1 ³⁷	0.396 (0.218-0.582)	
Description of exclusion criteria			
No	3 ^{28, 36, 37}	0.387 (0.272-0.508)	0
Yes	5 ^{9, 26, 27, 29, 30}	0.276 (0.184-0.378)	68
Specific criteria to define laryngeal dysfunction			
No	2 ^{26, 29}	0.202 (0.131-0.282)	4
Yes	6 ^{9, 27, 28, 30, 36, 37}	0.324 (0.216-0.442)	64
Type of stimulation			
Exercise	5 ^{9, 28, 30, 36, 37}	0.374 (0.280-0.482)	19
Other than exercise	3 ^{26, 27, 29}	0.198 (0.147-0.255)	0

95% CI, 95% confidence interval

Figure 1. Flowchart of the search strategy and study selection

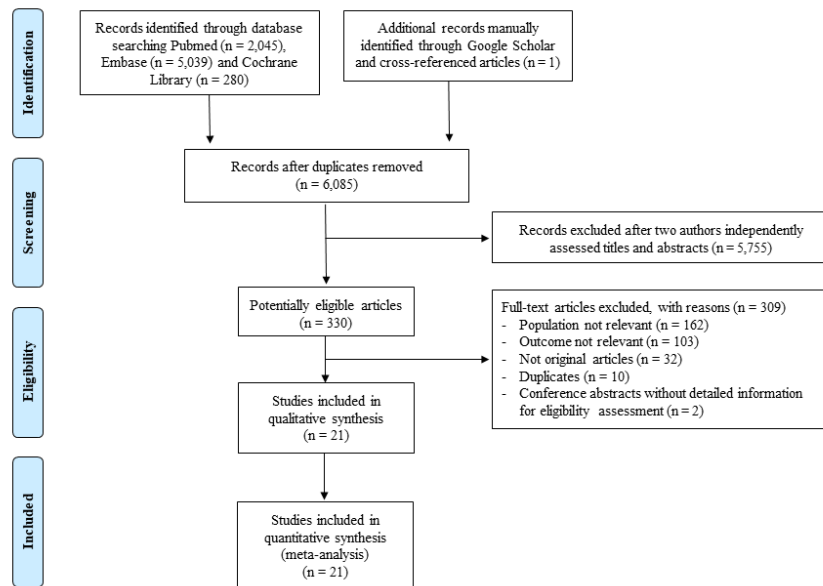


Figure 2. Forest plot of prevalence of laryngeal dysfunction in asthmatics

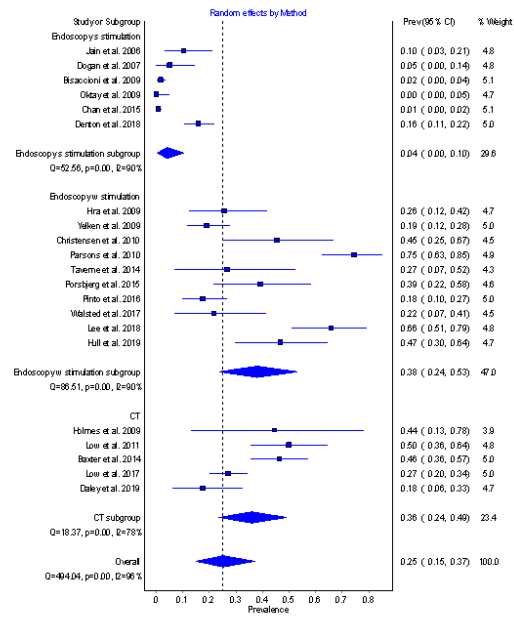
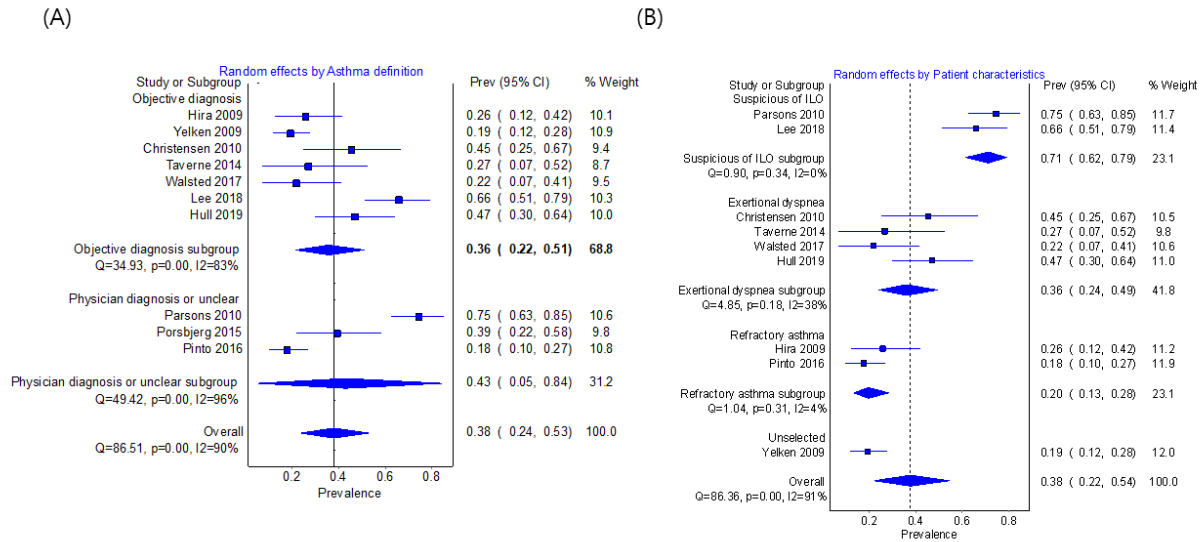
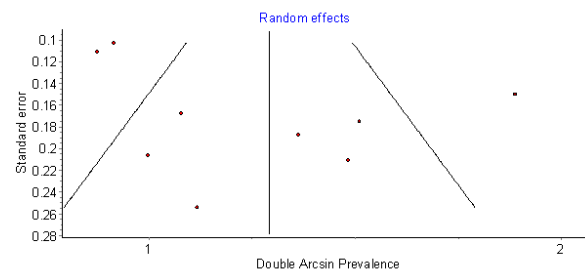


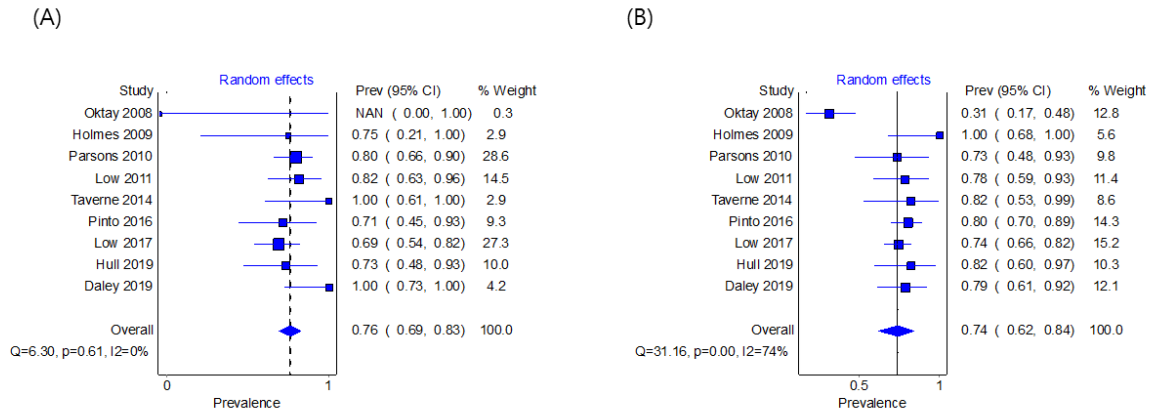
Figure 3. Subgroup analyses of prevalence of laryngeal dysfunction according to (A) asthma definitions utilized and (B) patient characteristics in 10 endoscopic studies utilizing external triggers



Supplementary Figure S1. Funnel plot of the prevalence of laryngeal dysfunction in 10 endoscopic studies utilizing external triggers



Supplementary Figure S2. Proportion of females among asthmatics with laryngeal dysfunction (A) and those without laryngeal dysfunction (B).



Online Supplement

Prevalence and impact of comorbid laryngeal dysfunction in asthma: A systematic review and meta-analysis

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Results

Study characteristics

Details in asthma definitions and patient selection criteria adapted in each study are summarized in Supplementary Table S2. Five studies¹⁻⁵ relied on physician's diagnoses (physician-diagnosed asthma), while the other studies⁶⁻²¹ defined asthma according to international guidelines or objective test results showing reversibility or hyper-responsiveness of the airway. Three studies^{1,3,16} were undertaken during an acute exacerbation of asthma-type symptoms. The severity and control status varied widely among the studies. Ten studies^{2,3,6,11,13,15-17,20,21} had defined exclusion criteria, which mainly consisted of structural problems of the larynx, cardiac or respiratory diseases, and other medical conditions prohibiting laryngoscopy .

Figure Legends

Supplementary Figure S1. Funnel plot of the prevalence of laryngeal dysfunction in 10 endoscopic studies with stimulation

Supplementary Figure S2. Proportion of females among asthmatics with laryngeal dysfunction (A) and those without laryngeal dysfunction (B).

41 **Supplementary Table S1. Search strategy**

Pubmed	
#1	"Asthma"[Mesh]
#2	asthma[Title/Abstract] OR asthmatic[Title/Abstract] OR asthmatics[Title/Abstract]
#3	Larynx[Mesh] OR Laryngeal Diseases[Mesh] OR "Voice Disorders"[Mesh:NoExp] OR Dysphonia[Mesh] OR Hoarseness[Mesh] OR Vocal Cord Dysfunction[Mesh] OR "Conversion Disorder"[Mesh]
#4	larynx[Title/Abstract] OR laryngeal[Title/Abstract] OR laryngitis[Title/Abstract] OR laryngismus[Title/Abstract] OR laryngomalacia[Title/Abstract] OR laryngospasm[Title/Abstract] OR "vocal cord"[Title/Abstract] OR "vocal cords"[Title/Abstract] OR "vocal fold"[Title/Abstract]
#5	#1 OR #2 OR #3 OR #4
Embase	
#1	'asthma'/exp
#2	asthma:ab,ti OR asthmatic:ab,ti OR asthmatics:ab,ti
#3	'larynx'/exp OR 'larynx disorder'/exp OR 'voice disorder'/exp OR 'conversion disorder'/exp
#4	larynx:ab,ti OR laryngeal:ab,ti OR laryngitis:ab,ti OR laryngismus:ab,ti OR laryngomalacia:ab,ti OR laryngospasm:ab,ti OR 'vocal cord':ab,ti OR 'vocal cords':ab,ti OR 'vocal fold':ab,ti OR voice:ab,ti OR dysphonia:ab,ti OR hoarseness:ab,ti OR 'conversion disorder':ab,ti OR 'globus pharyngeus':ab,ti OR 'globus pharyngis':ab,ti
#5	#1 OR #2 OR #3 OR #4

Supplementary Table S2. Summary of asthma definitions and patient selection criteria in the included studies

Study	Recruitment	Asthma condition	Exclusion criteria
Endoscopic studies without external trigger stimuli			
Jain et al. 2006. ³	- Prospective recruitment of patients with acute asthma exacerbation - ER, tertiary hospital; US	- Physician-diagnosed asthma - Presenting to ER with acute asthma exacerbation - Remained symptomatic despite albuterol nebulizer	- History of smoking (>10 pack-years) - Heart disease - Impending respiratory failure
Dogan et al. 2007 ²	- Prospective recruitment of patients with mild-to-moderate asthma - Outpatient clinic, university hospital; Turkey	- Physician-diagnosed asthma - Stable condition - Mild-to-moderate severity	- Smoking - Active upper respiratory tract infection - Age younger than 17 years - Pregnancy - Endotracheal intubation within 3 months of recruitment - History of laryngeal malignancy or surgery - History of radiotherapy of the head and neck or chemotherapy - Abnormal chest X-rays
Bisaccioni et al. 2009 ⁷	- Retrospective analysis of medical records of patients with severe persistent asthma - University hospital; Brazil	Severe persistent asthma according to the GINA criteria²²	No description
Oktay et al. 2009 ¹⁶	- Prospective recruitment of patients with acute asthma attack - ER, tertiary hospital; Turkey	- Asthma diagnosed according to the GINA criteria²² - Presenting to ER with acute asthma attack - Treated with bronchodilator and nasal oxygen	Medication use due to other systemic or upper respiratory tract diseases
Chan et al. 2015 ⁸	- Prospective recruitment of patients with severe asthma - University hospital; Singapore	Severe asthma diagnosed according to the WHO criteria²³	No detailed information (published in conference abstract)
Denton et al. 2018 ¹⁰	- Prospective consecutive recruitment of patients with difficult-to-treat asthma - Difficult asthma clinic, university hospital; Australia	- Asthma diagnosis based on the demonstration of variable airflow obstruction via bronchodilator response, peak flow variability, and/or bronchoprovocation testing and a consistent clinical history - Difficult-to-treat asthma with at least one of the following: severe or frequent asthma exacerbations despite treatment, inadequate control of asthma symptoms, unclear diagnosis, severe airflow obstruction, and/or complex management issues	None
Endoscopic studies with external trigger stimuli			
Hira et al. 2009 ¹¹	- Prospective recruitment of patients with refractory asthma - Tertiary hospital; India	- Asthma diagnosis based on significant reversibility of airway obstruction - Refractory asthma requiring high-dose oral steroids for the control of asthma symptoms or inconsistent response to bronchodilator therapy	- History suggestive of COPD, interstitial lung disease, chest wall deformities, and significant fibrosis or volume loss of lungs - Organic upper airway obstruction or identifiable cause of VCD (brainstem compression, myasthenia gravis, neurological injuries, or other causes)
Yelken et al. 2009 ²¹	- Prospective consecutive recruitment of asthma patients - Outpatient clinic, university hospital; Turkey	Asthma diagnosis based on typical symptoms with significant reversibility of airway obstruction	- Cardiac disease - Additional pulmonary disease
Christensen et al. 2010 ⁹	- Prospective recruitment of elite athletes with suspected asthma - Outpatient clinic, university hospital; Denmark	Asthma diagnosis based on symptoms and one of the following: reversibility min 10%, methacholine PD20 max 2.0 μmol, mannitol PD15 lower than 635 mg, or eucapnic hyperventilation test showing > 10% fall in FEV1	No detailed information (published in conference abstract)

Parsons et al. 2010 ⁵	• Prospective recruitment of asthmatic patients referred for videolaryngoscopy • Asthma center, university hospital; US	• Continued symptoms in spite of anti-asthma treatment • Physician-diagnosed asthma • Mild-to-moderate severity	• None
Taverne et al. 2014 ¹⁹	• Prospective recruitment of patients with poorly controlled asthma and unexplained exertional dyspnea • University hospital; France	• Asthma diagnosis based on positive bronchodilator response or methacholine bronchial provocation test	• None
Porsbjerg et al. 2015 ¹⁸	• Prospective consecutive recruitment of patients with verified asthma • Tertiary asthma clinic; Denmark	• Verified asthma (no detailed information; published in conference abstract)	• No detailed information (published in conference abstract)
Pinto et al. 2016 ¹⁷	• Consecutive recruitment of patients with severe asthma regardless of suspicion of VCD • University hospital; Brazil	• Severe asthma defined according to the WHO criteria²³	• Smokers • Laryngeal diseases unrelated to VCD
Walsted et al. 2017 ²⁰	• Prospective consecutive recruitment of patients with exertional dyspnea and possible asthma • Outpatient clinic, university hospital; Denmark	• Asthma diagnosis based on consistent symptoms and a positive BPT to either methacholine or mannitol in those with a baseline FEV1 of >70% of expected value; or in those with no BPT (i.e., if baseline FEV1 was ≤70%), asthma diagnosis based on a specialist evaluation considering symptoms, reversibility with bronchodilator, peak flow variation (>20%), and asthma history • Asthma with exercise-related symptoms	• Suspected EILO or VCD • Smoking history (>10 pack-years).
Lee et al. 2018 ¹⁴	• Prospective consecutive recruitment of referred patients with suspected ILO and asthma • Outpatient clinic, tertiary center; Australia	• Asthma diagnosis confirmed by demonstrating variable airflow obstruction based on bronchodilator response, peak flow variability >15%, or positive bronchial provocation challenge	• None
Hull et al. 2019 ¹³	• Prospective recruitment of patients with severe asthma and persistent exertional dyspnea • Tertiary hospital; UK	• Asthma diagnosis based on typical symptoms and either reversible airflow obstruction, bronchial hyper-responsiveness, or variable lung function over time • Severe asthma with persistent exertional dyspnea	• Contraindication to exercise testing and/or laryngoscopy • Current or past smoking history (>5 pack-years)
Larynx CT studies			
Holmes et al. 2009 ¹²	• Prospective evaluation of patients with severe long-standing asthma and suspected VCD • Outpatient clinic, tertiary center; Australia	• Asthma diagnosis according to the GINA criteria²² • Severe poorly controlled asthma with suspected VCD (tight throat, breathless after emotion or stress, brittle disease), 'noisy' sounds over the larynx, and relatively normal lung function	• None
Low et al. 2011 ¹⁵	• Prospective recruitment of patients with difficult-to-treat asthma • Severe asthma clinic, tertiary center; Australia	• Asthma diagnosis based on typical symptoms with positive bronchodilator response or documented asthma exacerbation • Difficult-to-treat asthma (1) with chronic severe breathlessness, lack of response to treatment with high-dose ICS/LABA combinations, and requiring frequent courses of OCS, or (2) with episodic severe breathlessness not responsive to optimized ICS/LABA combinations	• COPD or other lung disease, smoking history greater than 10 pack-years, vocal cord pathology (e.g., laryngeal cancer), neurological disease, and pregnancy
Baxter et al. 2014 ⁶	• Prospective recruitment of patients with refractory asthma • Severe asthma clinic, tertiary center; Australia	• Asthma diagnosed according to the GINA criteria²² • Refractory asthma, severely symptomatic (ACT score <16) despite optimized management including verified adherence)	• Other laryngeal disease
Low et al. 2017 ⁴	• Prospective recruitment of patients with asthma symptoms • Outpatient clinic, tertiary center with	• Asthma diagnosis based on: (1) a typical past history of asthma symptoms, (2) favorable clinical responses to treatment with beta-agonists and/or ICSs and (3) a diagnosis of asthma by their general	• None

	collaboration of general practice and severe asthma clinics; Australia	practitioner	
Daley et al. 2019 ¹	• Prospective recruitment of patients with acute asthma exacerbation • ER, tertiary hospital; Australia	• Physician-diagnosed asthma • Presenting to ER with acute asthma exacerbation • CT conducted soon after the initial stabilization of the patient	• None

ER, emergency room; GINA, Global Initiative for Asthma; WHO, World Health Organization; COPD, chronic obstructive pulmonary disease; VCD, vocal cord dysfunction; FEV1, forced expiratory volume in 1 second; PD20, provocation dose to cause a 20% decrease in FEV1; PD15, provocation dose to cause a 15% decrease in FEV1; BPT, bronchial provocation test; EILO, exercise-induced laryngeal obstruction; ILO, inducible laryngeal obstruction; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; OCS, oral corticosteroids; ACT, asthma control test

Supplementary Table S3. Quality assessment

Study	Prospective recruitment (0: no; 1: yes)	Sample size justification (0: no; 1: yes)	Population definition (asthmatic) (0: physician diagnosis; 1: objective evidence)	Sample representativeness (0: recruited at a single center; 1: recruited at multiple centers; 2: recruited from general populations)	Risk of selection bias (0: recruited for suspected laryngeal dysfunction; 1: recruited for respiratory symptoms; 2: unselected recruitment; 9: unclear)	Description of exclusion criteria (0: no; 1: yes)	Outcome definition (laryngeal dysfunction) (0: no specific criteria presented; 1: specific criteria)
Endoscopic studies without external trigger stimuli							
Jain et al. 2006 ³	1	0	0	0	1	1	1
Dogan et al. 2007 ²	1	0	0	0	2	1	0
Bisaccioni et al. 2009 ⁷	0	0	0	0	1	0	1
Oktay et al. 2009 ¹⁶	1	0	0	0	1	1	0
Chan et al. 2015 ⁸	1	0	0	0	1	0	0
Denton et al. 2018 ¹⁰	1	0	1	0	1	0	0
Endoscopic studies with external trigger stimuli							
Hira et al. 2009 ¹¹	1	0	1	0	1	1	0
Yelken et al. 2009 ²¹	1	0	1	0	2	1	1
Christensen et al. 2010 ⁹	1	0	1	0	1	0	1
Parsons et al. 2010 ⁵	0	0	0	0	0	0	1
Taverne et al. 2014 ¹⁹	1	0	1	0	1	0	1
Porsbjerg et al. 2015 ¹⁸	1	0	0	0	9	0	1
Pinto et al. 2016 ¹⁷	1	0	0	0	1	1	0
Walsted et al. 2017 ²⁰	1	0	1	0	1	1	1
Lee et al. 2018 ¹⁴	1	0	1	0	0	0	1
Hull et al. 2019 ¹³	1	0	1	0	1	1	1
Larynx CT studies							
Holmes et al. 2009 ¹²	1	0	0	0	0	0	1
Low et al. 2011 ¹⁵	1	0	1	0	1	1	1
Baxter et al. 2014 ⁶	1	0	1	0	1	1	1
Low et al. 2017 ⁴	1	0	0	1	2	0	1
Daley et al. 2019 ¹	1	0	0	0	2	0	1

CT, computed tomography

Supplementary Table S4. Sensitivity analyses of 10 endoscopic studies with external trigger stimuli

Parameter	Number of studies	Prevalence of laryngeal dysfunction (95% CI)	I ² (%)
Study design			
Prospective	9 ^{9,11,13,14,17-21}	0.334 (0.223-0.459)	82
Retrospective	1 ⁵	0.746 (0.626-0.580)	
Description of patient exclusion criteria			
No	5 ^{5,9,14,18,19}	0.539 (0.330-0.742)	83
Yes	5 ^{11,13,17,20,21}	0.276 (0.184-0.378)	68
Specific criteria to define laryngeal dysfunction			
No	2 ^{11,17}	0.202 (0.131-0.282)	4
Yes	8 ^{5,9,13,14,18-21}	0.426 (0.256-0.604)	89
Type of stimulation			
Exercise	6 ^{5,9,13,18-20}	0.436 (0.263-0.616)	82
Other than exercise	4 ^{11,14,17,21}	0.301 (0.117-0.522)	91

Supplementary Table S5. Summary of asthma outcomes associated with laryngeal dysfunction in patients with asthma (vs. those without laryngeal dysfunction)

Study	Asthma outcome		
	Asthma severity (severity classification)	Asthma control (measurement scale)	Asthma-related QoL
Endoscopic studies without external trigger stimuli			
Jain et al. 2006 ³	NR	NR	NR
Dogan et al. 2007 ²	NR	NR	NR
Bisaccioni et al. 2009 ⁷	NR	NR	NR
Oktay et al. 2009 ¹⁶	NR	NR	NR
Chan et al. 2015 ⁸	NR	NR	NR
Denton et al. 2018 ¹⁰	NA (only patients with difficult-to-treat asthma included)	NR	NR
Endoscopic studies with external trigger stimuli			
Hira et al. 2009 ¹¹	NR	NR	NR
Yelken et al. 2009 ²¹	No significant association (intermittent, mild persistent, moderate persistent, or severe persistent ²²)	NR	NR
Christensen et al. 2010 ⁹	NR	NR	NR
Parsons et al. 2010 ⁵	Significant association (intermittent, mild persistent, moderate persistent, or severe persistent ²⁴)	Significant association (ATAQ)	NR
Taverne et al. 2014 ¹⁹	No significant association (step 3/4 vs. 5 ²²)	No significant association (ACT)	NR
Porsbjerg et al. 2015 ¹⁸	NR	NR [*]	NR
Pinto et al. 2016 ¹⁷	NA (only patients with severe asthma included ²³)	NR	NR
Walsted et al. 2017 ²⁰	NR	NR ^{**}	NR ^{**}
Lee et al. 2018 ¹⁴	NR	NR	NR
Hull et al. 2019 ¹³	NA (only patients with severe asthma included ²⁵)	No significant association (ACT)	NR
Larynx CT studies			
Holmes et al. 2009 ¹²	NA (only patients with severe persistent asthma included ²²)	NR	NR
Low et al. 2011 ¹⁵	No significant association (mild persistent, moderate persistent, or severe persistent ²²)	No significant associations (ACT, ACQ)	NR
Baxter et al. 2014 ⁶	NR	NR	NR
Low et al. 2017 ⁴	No significant association (non-severe vs. severe ²⁵)	No significant associations (ACT, ACQ5)	NR
Daley et al. 2019 ¹	No significant association (mild-moderate vs. severe ²²)	NR	NR

NR, not reported; NA, not available for comparison; QoL, quality of life; GINA, Global Initiative for Asthma; EPR3, Expert Panel Report 3²⁴; ATS, American Thoracic Society; ERS, European Respiratory Society; ATAQ, Asthma Therapy Assessment Questionnaire; ACT, asthma control test; ACQ, asthma control questionnaire; ACQ5, asthma control questionnaire 5-item version

*No detailed results (abstract only study); **Not assessed for asthmatics only

Supplementary Table S6. Summary of specific symptoms associated with laryngeal dysfunction in patients with asthma (vs. those without laryngeal dysfunction)

Study	Stridor	Choking	Dysphonia (or hoarseness)	Wheezing	Dyspnea	Coughing	Night symptoms	Chest tightness	Difficulty in breathing	Dysfunctional breathing
Endoscopic studies without external trigger stimuli										
Jain et al. 2006 ³	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Dogan et al. 2007 ²	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bisaccioni et al. 2009 ⁷	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Oktay et al. 2009 ¹⁶	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chan et al. 2015 ⁸	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Denton et al. 2018 ¹⁰	NR	NR	NR	NR	NR	NR	NR	NR	NR	No significant association (12 of 25 vs. 61 of 132)*
Endoscopic studies with external trigger stimuli										
Hira et al. 2009 ¹¹	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Yelken et al. 2009 ²¹	Positive association (12 of 18 vs. 12 of 76)	Positive association (9 of 18 vs. 4 of 76)	Positive association (8 of 18 vs. 10 of 76)	Negative association (4 of 18 vs. 39 of 76)	Negative association (4 of 18 vs. 42 of 76)	No significant association (9 of 18 vs. 48 of 76)	NR	NR	Positive association (16 of 18 vs. 18 of 76)	NR
Christensen et al. 2010 ⁹	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Parsons et al. 2010 ⁵	No significant association (2 of 44 vs. 0 of 15)	NR	No significant association (9 of 44 vs. 3 of 15)	Positive association (1.18 vs. 0.53)**	Positive association (1.77 vs. 0.87)**	Positive association (1.57 vs. 0.60)**	No significant association (1.1 vs. 1.00)**	NR	NR	NR
Taverne et al. 2014 ¹⁹	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Porsbjerg et al. 2015 ¹⁸	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pinto et al. 2016 ¹⁷	Positive association (13 of 14 vs. 15 of 29)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Walsted et al. 2017 ²⁰	NR***	NR***	NR***	No significant associations*** 1) wheezing at rest (1 of 8 vs. 13 of 29) 2) wheezing	NR***	NR***	NR***	NR***	NR***	No significant association (4 of 11 vs. 7 of 36)*,***

				during exercise (3 of 8 vs. 9 of 19)						
Lee et al. 2018 ¹⁴	Positive association (21 of 29 vs. 5 of 15)	No significant association (18 of 29 vs. 6 of 15)	NR	No significant association (23 of 29 vs. 11 of 15)	NR	No significant association (19 of 29 vs. 10 of 15)	NR	No significant association (27 of 29 vs. 13 of 15)	No significant association (18 of 29 vs. 7 of 15)	NR
Hull et al. 2019 ¹³	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Larynx CT studies										
Holmes et al. 2009 ¹²	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Low et al. 2015 ¹⁵	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Baxter et al. 2014 ⁶	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Low et al. 2017 ⁴	NR	NR	NR	NR	NR	NR	NR	NR	NR	Positive association (7 of 11 vs. 4 of 19) ^{****}
Daley et al. 2019 ¹	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

¹Defined by a positive Nijmegen Questionnaire score (greater than 23) and accompanied by compatible clinical symptoms including excessive dyspnea¹⁰

^{**}Reported in scale (0 = none, 1 = ≤2/week, 2 = >2/week, 3 = daily, 4 = continuous)

^{***}Data from subjects recruited for exertional dyspnea and possible asthma (62% of them were diagnosed with asthma based on symptoms as well as bronchial challenge tests)²⁰

^{****}Defined by a positive Nijmegen Questionnaire score (greater than 20)

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