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REVIEW

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The impact of identifying laryngeal obstruction syndromes on reducing treatment of pediatric asthma: A systematic review

Caseng Zhang[1] | Matt Hicks MD, PhD[2] | Maria B. Ospina PhD[3] | Vishnu Martha MD, PhD[4] | Ghiath Alnouri MD[4] | Liz Dennett MLIS[5] | Robert Sataloff MD, DMA[4] | Anne Hicks MD, PhD[2]

[1]Faculty of Health Sciences, McMaster University, Hamilton, Canada

[2]Department of Pediatrics, University of Alberta, Edmonton, Canada

[3]Department of Obstetrics and Gynecology, University of Alberta, Edmonton, Canada

[4]Department of Otolaryngology, Head and Neck Surgery, Drexel University College of Medicine, Philadelphia, Pennsylvania, USA

[5]John W. Scott Health Sciences Library, University of Alberta, Edmonton, Canada

Correspondence
Anne Hicks, MD, PhD, Department of Pediatrics, University of Alberta, 11405 87 Ave, Edmonton, AB T6G 1C9, Canada.
Email: eagreene@ualberta.ca

Abstract

Inducible laryngeal obstruction (ILO) in children is underrecognized. This systematic review characterizes the scientific evidence on the impact of pediatric ILO diagnosis and treatment on asthma medication use. This review, registered with PROSPERO (CRD42020209168), utilized database searches in MEDLINE, EMBASE, CINAHL, and Web of Science from inception to October 2020. Both experimental and observational studies on ILO and asthma outcomes in patients ≤18 years were included. Population characteristics (sample size, sex, age, and comorbidities) and study outcomes (medication usage and respiratory symptoms) were extracted. The risk of bias was assessed with the National Toxicology Program's Office of Health Assessment and Risk of Bias Rating Tool. Data are presented narratively due to study heterogeneity. Of 1091 studies, 1076 titles and abstracts were screened after duplicate removal. Screening 31 full texts yielded eight pre–post studies. Patients were an average of 14.1 years old, 15% male, and >90% used asthma medication; 40% reported allergies, 30% gastroesophageal reflux, and 20% anxiety or depression. Most patients received at least one intervention, with 75% showing symptomatic improvement and >75% decreasing or stopping asthma medications. Studies were small with a high risk of selection, confounding, and detection bias. Asthma management was not a primary outcome in any of the studies. Overall, ILO patients were often diagnosed with or treated for asthma before ILO diagnosis. Evidence from individual studies suggests that comorbidities including ILO, gastroesophageal reflux, allergies, and anxiety should be considered in pediatric patients with asthma not responsive to medical therapy. Further research is required to determine the proportion of impacted asthma patients.

KEYWORDS

asthma, exercise-induced laryngeal obstruction, inducible laryngeal obstruction, paradoxical vocal fold motion, pediatrics, vocal cord dysfunction

This study has been presented as a poster at the American Thoracic Society Annual General Meeting (Virtual) 2021.

1 | INTRODUCTION

Asthma, the most common respiratory chronic disease in childhood, causes considerable morbidity in the pediatric population.[1] Treatment, particularly with inhaled corticosteroids (ICS), introduces the risk of side effects including reduced growth velocity and adult height, elevated body mass index, adrenal suppression, dysphonia, thyroarytenoid muscle atrophy, and local *Candida* infection.[2–5]

Asthma can be a misdiagnosis or comorbid condition for inducible laryngeal obstruction (ILO), a laryngeal disorder characterized by inappropriate vocal fold (VF) adduction during the respiratory cycle.[6] Commonly used terms have evolved over time, from vocal cord dysfunction (VCD) and paradoxical VF motion to the physiologic descriptive term ILO. A subset of asthmatic adults have been diagnosed with ILO; the converse is also true and in one study up to 63% of adults with ILO have been diagnosed with asthma.[7] Typical ILO symptoms include stridor, wheeze, and cough. Phenotypically these can occur spontaneously (SILO), be induced by exercise (EILO), or have a mixed presentation.[8] In one study of 99/146 adolescents reporting exercise-induced dyspnea, 19% had asthma and nearly 6% had EILO, with about 2/3 of the EILO patients showing overlap.[9] Misdiagnosis can be costly. A 2016 U.S. study showed that ILO patients were treated for asthma for an average of 9 years with monthly medication costs of USD $136.40–$256.90 plus $566 in excess emergency visits.[7]

The gold standard for ILO diagnosis is visualizing abnormal VF adduction during laryngoscopy.[10] Paradoxical electrical activity on laryngeal electromyography can detect ILO but is not recommended in children due to the need for anesthesia.[11,12]

Treatment includes VF abduction exercises, training with a speech-language pathologist (SLP), or behavioral therapy.[10] Inhaled anticholinergic (ipratropium bromide) is used to treat EILO, based on the premise that vagus nerve stimulation and a dysautonomic response to respiratory irritants may trigger symptoms.[13,14] Local botulinum toxin injection can lead to improvement in selected adult patients,[15] but has not been demonstrated in children. This systematic review evaluated the scientific evidence on the effects of diagnosing and treating ILO on asthma medication use and respiratory symptoms among pediatric patients.

2 | METHODS

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[16,17] (Table S3). The study protocol was registered with PROSPERO (CRD42020209168).

2.1 | Search strategy

Comprehensive searches of biomedical databases MEDLINE, Embase (Ovid interface), CINAHL Plus with Full Text (EBSCO host interface), and Web of Science Core Collection were conducted from database

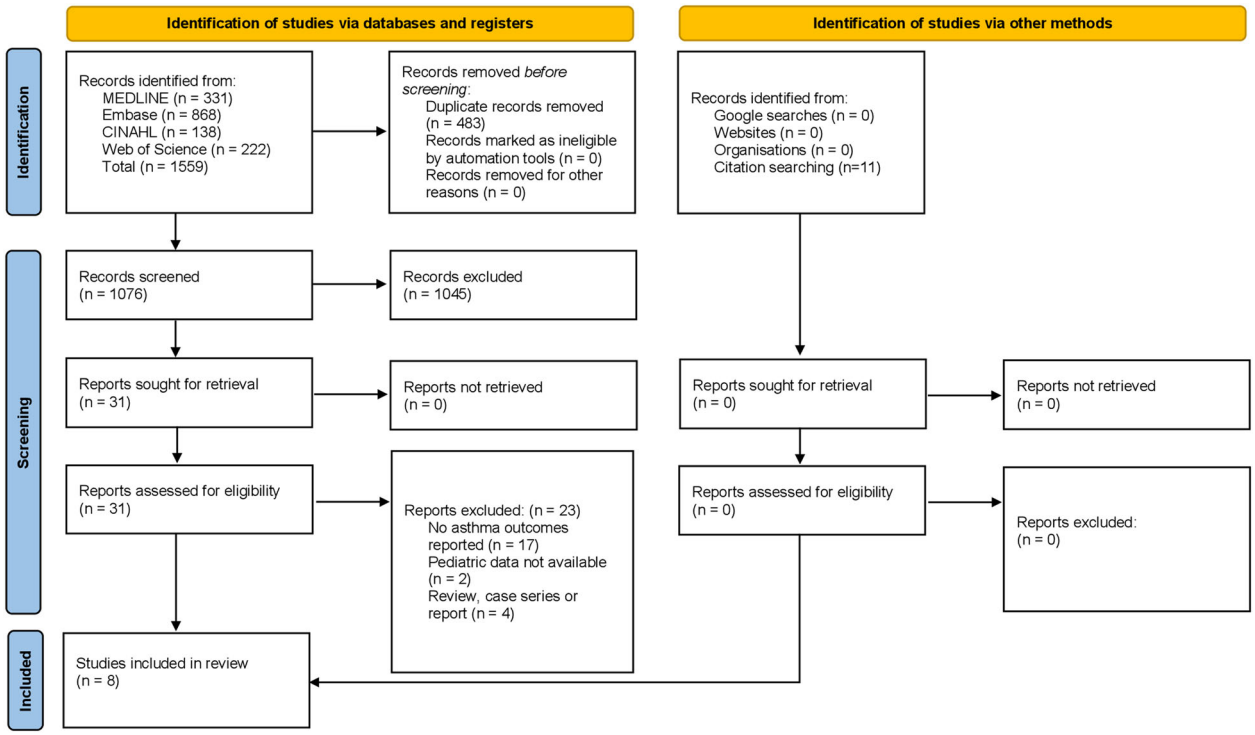

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses flow diagram for pediatric inducible laryngeal obstruction and asthma resulting from searches of databases, registries, and other sources[17] [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Characteristics of individual studies included in the review

Study	Study characteristics	Population characteristics	Symptoms at evaluation	Intervention characteristics	Intervention and comparison groups	Outcomes	Follow-up
Doshi et al.[22]	Study design: Observational cohort Enrollment: 1989–2002 Method: Retrospective chart review and follow-up survey Setting: University of Iowa Pediatric Asthma and Allergy Clinic Funding: No external funding Strengths: Individual data reported in detail Challenges: Participation, memory bias	*N* = 28 Sex: 18 (65%) F Mean age (SD) (year): 13.7 (2.5) Country: USA Other characteristics: Descriptive study of ILO in adolescent patients; 28/48 participated, 23/28 had a presumed asthma diagnosis	Prestudy formal asthma diagnosis: 23 (82%) Inhaler use: 23 (82%) Stridor: not reported Dysphonia: Not reported Any dyspnea: Not reported Any exertional dyspnea 20/28 (71%) Exertional dyspnea only: 17/28 (60%) Psychological dyspnea: 8/28 (29%) >1 trigger dyspnea: 3 (11%) Comorbidities: Not reported	Presumed ILO: 23/23 Confirmed ILO (laryngoscopy): 15/23 Information only: 10/23 SLP: 8/23 Other behavioral therapy: No Ipratropium bromide: 5/23 Botulinum toxin: No Formal asthma diagnosis: Spirometry	Preintervention: 23/28 (82%) presumed asthma Postintervention: 15/23 (65%) received laryngoscopy; 8/23 (35%) received SLP	Medication decrease: 19/23 (83%) Medication stopped: Not reported Respiratory symptom decrease: 14/23 (61%) Comorbidity: Not reported Other: 6/23 (26%) decreased exercise Ipratropium bromide was offered for EILO	0.5–12 years
Fulton et al.[23]	Study design: Observational cohort Method: Retrospective chart review Enrollment: January 1 to December 31, 2016 Setting: Oregon Health and Science University Department of Otolaryngology Funding: No external funding Strengths: Laryngoscopy for all participants Challenges: Primary outcome was dysphonia	*N* = 48 Sex: 35 (73%) F Mean age (SD) (year): 14.5 (2.1) Country: USA Other characteristics: Descriptive study of adolescent dysphonia, 31/48 ILO (65%) with a prestudy asthma diagnosis	Prestudy formal asthma diagnosis: 31/48 (65%) Inhaler use: 31/48 (65%) Stridor: Not reported Dysphonia: 25/48 (52%) Any dyspnea: 48 (100%) Any exertional dyspnea 47/48 (98%) Exertional dyspnea only: Not reported Psychological dyspnea: 10/48 (20%) >1 trigger dyspnea: 9/48 Comorbidities: GERD 2 (6%); Allergy 22 (71%); Swallowing dysfunction 4 (8%)	Presumed: 31/31 Confirmed ILO (laryngoscopy): 31/31 (100%) Information only: None SLP: 31/31 (100%) Other behavioral therapy: None Ipratropium bromide: None Botulinum toxin: None Formal asthma diagnosis: Not reported	Preintervention: 31/48 (65%) presumed asthma Postintervention: 48/48 (100%) received laryngoscopy, 48/48 (100% received SLP	Medication decrease: Not reported Medication stopped: Not reported Respiratory symptom decrease: 31/31 (100%) Comorbidity: 1 GERD Other: 24/48 (50%) had dysphonia; 3/48 (6%) had structural abnormalities—vocal fold nodules	Follow-up therapy visits in 33 (69%) ranging from 1 to 6 additional visits; timeline not reported
Hseu et al.[24]	Study design: Observational cohort	*N* = 270 Sex: 74% F	Prestudy formal asthma diagnosis: 107	Presumed ILO: 11/107 (10%)	Preintervention: 270 had cardiorespiratory	Medication decrease: 77/107 (72%)	Not reported

(Continues)

TABLE 1 (Continued)

Study	Study characteristics	Population characteristics	Symptoms at evaluation	Intervention characteristics	Intervention and comparison groups	Outcomes	Follow-up
	Method: Retrospective chart review Enrollment: January 2007 to July 2015 Setting: Boston Children's Hospital Exercise Clinic Funding: No external funding Strengths: Large cohort, all participants received laryngoscopy, exercise challenge, pulmonary function testing Challenges: Individual outcomes and asthma medication use unclear	Mean age (SD) (year): 14.6 Country: USA Other characteristics: 294 evaluated, 290 complete charts, 107 (37%) with presumed asthma t; descriptive study enumerating causes of exertional dyspnea	Inhaler use: 105 Stridor: 151 (56%) Dysphonia: 11 (4%) Any dyspnea: 251 (93%) Any exertional dyspnea: Not reported Exertional dyspnea only: Not reported Psychological dyspnea: not reported >1 trigger dyspnea: Not reported Comorbidities: GERD 62 (23%); anxiety 50 (17%), Allergy 89 (33%)	Confirmed ILO (laryngoscopy): 86/107 (80%) Information only: None SLP: 86/107 (80%); of total 116/270 (40%) Other behavioral therapy: None Ipratropium bromide: 77/270 (27%) Botulinum toxin: None Formal asthma diagnosis: 30/107 (28%)	treadmill challenge; pretest 107 (37%) had asthma or suspected asthma; 209 (72%) exertional dyspnea Postintervention: Of presumed asthma patients 86/107 (80%) received laryngoscopy, 86/107 (80%) received SLP	Medication stopped: 77/107 (72%) Respiratory symptom decrease: not reported Comorbidity: Not reported Other: 7 (7%) increased exercise after evaluation	
Rameau et al.[25]	Study design: Case series Method: Retrospective chart review and telephone interview Enrollment: October 2007 to April 2009 Setting: The Children's Hospital of Philadelphia Voice and Airway Clinics Funding: No external fundding Strengths: Individual data reported in detail Challenges: Type of asthma medication not identified	*N* = 22 Sex: 16 (73%) Mean age (SD) (year): 13.4 Country: USA Other characteristics: 22/40 patients completed interviews; objectives were to evaluate whether one-visit diagnosis and treatment improves ILO symptoms and describe the prevalence of comorbidities including asthma	Prestudy formal asthma diagnosis: 15 (68%) Inhaler use: Ever 18 (82%); at enrollment 15 (68%) Stridor: Dysphonia: not described Any dyspnea: 22 (100%) Any exertional dyspnea: 19 (86%) Exertional dyspnea only: 15 (68%) Psychological dyspnea: 2 (9%) >1 trigger dyspnea: 1 Comorbidities: GERD 13 (59%); allergy 14 (64%); emotional distress 3 (14%); Lyme-related dysautonomia 1 (5%)	Presumed ILO: 22/22 (100%) Confirmed ILO (laryngoscopy): 22/22 (100%) Information only: None SLP: 22/22 (100%) Other behavioral therapy: none Ipratropium bromide: Not reported Botulinum toxin: none Formal asthma diagnosis: Not reported	Preintervention: 15/22 (68%) patients had a provisional asthma diagnosis Postintervention: 22/22 (100%) received laryngoscopy; 22/22 (100% received SLP)	Medication decrease: 9/15 (60%) Medication stopped: 6/15 (40%) Respiratory symptom decrease: 15/15 (100%); only 2/15 (13%) had resolution Comorbidity: Not reported Other: 11/22 (50%) increased activity level after treatment	14 (SD 7.2) months

TABLE 1 (Continued)

Study	Study characteristics	Population characteristics	Symptoms at evaluation	Intervention characteristics	Intervention and comparison groups	Outcomes	Follow-up
Sullivan et al.[26]	Study design: Observational cohort Method: Prospective observational cohort study Enrollment: 20 consecutive referrals, enrollment period not reported Setting: Pediatric Pulmonology, Allergy and Clinical Immunology, and Otorhinolaryngology, Clinics at the University of Nebraska Medical Centre and the Munroe-Meyer Institute (Nebraska) Funding: MCJ 319152 Maternal and Child Bureau, Health Resources Services Administration and 90DD0324 from the American Association of University Affiliated Programs for Persons With Developmental Disabilities Strengths: Prospective cohort study, detailed breakdown of individual characteristics Challenges: Sex/gender bias with only female athletes included	*N* = 20 Sex: 20 (100%) F Mean age (SD) (year): 14.1 Country: USA Other characteristics: Descriptive analysis of presentation and treatment of adolescent female athletes with ILO	Prestudy formal asthma diagnosis: Not reported Inhaler use: 19 (95%) Stridor: 20 (100%) Dysphonia: Not reported Any dyspnea: 20 (100%) Any exertional dyspnea 20 (100%) Exertional dyspnea only: 15 (75%) Psychological dyspnea: 5 (25%) >1 trigger dyspnea: 5 (25%) Comorbidities: GERD 1 (5%); allergy 6 (30%), diabetes 1 (5%)	Presumed ILO: 20/20 (100%) Confirmed ILO (laryngoscopy): 20/20 (100%) Information only: None SLP: 20/20 (100%) Other behavioral therapy: None Ipratropium bromide: Not reported Botulinum toxin: None Formal asthma diagnosis: Not reported	Preintervention: 19/20 (95%) with suspected asthma Postintervention: 20/20 (100% received laryngoscopy, 20/20 received SLP	Medication decrease: 19/19 (100%) Medication stopped: 16/19 (84%) Respiratory symptom decrease: 14/20 (70%) Comorbidity: Not reported Other: All athletes, no loss of participation during study	6 months
Vance et al.[27]	Study design: Observational cohort Enrollment: January 12007 to August 31 2019 Method: Retrospective chart review Setting: Drexel University College of Medicine Department of Otolaryngology Funding: No external funding	*N* = 13 Sex: 10 F (77%) Mean age (SD) (year): 14.7 (1.7) Country: USA Other characteristics: 18/40 pediatric patients, 13 with a provisional diagnosis of asthma descriptive review	Prestudy formal asthma diagnosis: not reported Inhaler use: 13 (100%) Stridor: not reported Dysphonia: 13 (100%) Any dyspnea: 100% Any exertional dyspnea: not reported Exertional dyspnea only: not reported	Presumed ILO): 13/13 (100%) Confirmed ILO (laryngoscopy): 11/13 (85%) Information only: None SLP: 11/13 (85%) Other behavioral therapy: None	Preintervention: 13/13 (100%) pediatric patients in a mixed adult/pediatric study with possible ILO and asthma Post-intervention: 11/13 (85%) received laryngoscopy; 11/13 (85%) received SLP; 6/13 (46%) received botox; 4/13 (31%) received both	Medication decrease: Not reported Medication stopped: Not reported Respiratory symptom decrease: 8/13 (62%) Comorbidity: GERD Other: Dysphonia improved when treated	Not reported

(Continues)

TABLE 1 (Continued)

Study	Study characteristics	Population characteristics	Symptoms at evaluation	Intervention characteristics	Intervention and comparison groups	Outcomes	Follow-up
	Strengths: Detailed patient information available from authors Challenges: Primary outcome was dysphonia		Psychological dyspnea: not reported >1 trigger dyspnea: not reported Comorbidities: GERD 11 (85%); Anxiety 3 (23%); Allergy 8 (62%)	Ipratropium bromide: Not reported Botulinum toxin: 6/13 (46%) Formal asthma diagnosis: Not done			
Yibrehu et al.[28]	Study design: Observational cohort Method: Retrospective chart review and follow-up survey Enrollment: 2006–2017 Setting: Children's National Hospital Health System, Washington DC Funding: No external funding Strengths: Broad chart review to identify potential participants Challenges: Participation and recall bias	*N* = 18 Sex: 14 (78%) Mean age (SD) (year): 11.6 (2.3) Country: USA Other characteristics: Limited to >8 years old; descriptive study; 2 Asian, 6 Black, 10 White	Prestudy formal asthma diagnosis: Not reported Inhaler use: 14/18 (78%) Stridor: 9 (50%) Dysphonia: Not reported Any dyspnea: 16 (89%) Any exertional dyspnea: 8 (44%) Exertional dyspnea only: Not reported Psychological dyspnea: 14 (78%) >1 trigger dyspnea: Not reported Comorbidities: Globus 10 (56%), GERD 8 (44%), allergy 4 (22%); stress 6 (33%)	Presumed ILO: 18/18 (100%) Confirmed ILO (laryngoscopy): 18/18 (100%) Information only: Not reported SLP: 16/18 (89%) Other behavioral therapy: 8/18 (44%) Ipratropium bromide: 10/18 (56%) Botulinum toxin: None reported Formal asthma diagnosis: Not reported	Preintervention: 47 patients with suspected ILO; 21 (45%) responded, 18 (38% of total; 86% of responders) completed survey Postintervention: 18/18 (100%) received laryngoscopy; 16/18 (89%) received SLP	Medication decrease: 14/14 (100%) Medication stopped: 12/14 (86%) Respiratory symptom decrease: 14/18 (78%) Comorbidity: 7/18 (19%) GERD Other: Decrease in perceived stress post treatment; no change to grades or physical activity	Mean 3.4 years
Ivancic et al.[29]	Study design: Prospective cohort Method: Prospective enrollment Enrollment: November 2015 to June 2018 Setting: Nationwide Children's Hospital Voice and Swallowing Disorders Clinic, Columbus Ohio Funding: No external funding	*N* = 26 Sex: 21 (85%) F Median age (SD) (year): 14 Country: USA Other characteristics: Primary objective was whether diagnosis of ILO in adolescents decreased asthma medication use	Prestudy formal asthma diagnosis: 19 (73%) Inhaler use: 26 (100%) Stridor: 16 (62%) Dysphonia: not reported Any dyspnea: 26 (100%) Any exertional dyspnea 23 (88%) Exertional dyspnea only: 13 (50%)	Presumed ILO: 26/26 (100%) Confirmed ILO (laryngoscopy): 26/26 (100%) Information only: 5/26 SLP: 21/26 Other behavioral therapy: Not reported	Preintervention: 19/26 (73%) patients had a provisional asthma diagnosis Postintervention: 26/26 (100%) patients received laryngoscopy; 21/26 (81%) received SLP	Medication decrease: 15/19 (79%) Medication stopped: Not reported Respiratory symptom decrease: Not reported Comorbidity: 11/26 (42%) treated for GERD	8–42 months

TABLE 1 (Continued)

Study	Study characteristics	Population characteristics	Symptoms at evaluation	Intervention characteristics	Intervention and comparison groups	Outcomes	Follow-up
	Strengths: Prospective cohort study, laryngoscopy for all participants Challenges: No spirometry		Psychological dyspnea: 16 (62%) >1 trigger dyspnea: 10 38% Comorbidities: GERD 12 (46%); Allergy 17 (65%) Dysphagia 7 (27%)	Ipratropium bromide: Not reported Botulinum toxin: None Formal asthma diagnosis: Not reported		Other: Patients with the highest dyspnea score were most likely to complete two SLP sessions and least likely to stop asthma medication	

Abbreviations: EILO, exercise-induced laryngeal obstruction; F, female; GERD, gastroesophageal reflux disease; ILO, inducible laryngeal obstruction; SLP, speech-language pathologist.

inception to October 2020. The search strategy included selected subject headings and keyword synonyms related to ILO treatment and asthma (see Supporting Information). No date or language or publication limits were used. Reference lists of included articles and reviews were screened for relevant studies. Google and Google Scholar search, contacts with experts in the field, and patient and physician resources published by the American Thoracic Society, Canadian Thoracic Society, British Thoracic Society, and European Respiratory Society were reviewed to identify additional studies.

2.2 | Eligibility criteria

Peer-reviewed primary studies on ILO, asthma, and pediatric health outcomes were evaluated. Articles included in the study population reported children (5–18 years) with a presumed diagnosis of asthma and suspected diagnosis of ILO. All papers that had full text available in English (original or translatable by Google Translate) were included, as translation services were not feasible for this review. Both experimental and observational studies were considered; however, case reports were excluded. Articles were excluded if the study population had no diagnosis of asthma, no diagnosis of ILO, results for children were not available, or the study had no reported asthma or respiratory symptom outcomes. The primary outcome of interest was the proportion of participants who stopped or decreased asthma medication. The secondary outcome was the proportion of participants who had a change in respiratory symptoms after treatment. A provisional diagnosis of asthma was based on the study authors' evaluation of a prior asthma diagnosis; this was assumed if patients were reported as using asthma medication at the time of study enrollment.

2.3 | Study selection

Titles and abstracts retrieved from the search were screened independently by two pairs of reviewers (Caseng Zhang and Anne Hicks, or Vishnu Martha and Ghiath Alnouri), and study authors were contacted for additional information as required. Full texts of relevant articles were retrieved and screened independently by the same four reviewers to determine eligibility. Disagreements were resolved through discussion among reviewers until a consensus was reached. A PRISMA flow diagram was prepared based on the results (Figure 1).

2.4 | Risk of bias

Two pairs of independent reviewers (Caseng Zhang and Anne Hicks, or Vishnu Martha and Ghiath Alnouri) assessed the risk of bias in all included studies using the Office of Health Assessment and Translation (OHAT) Risk of Bias Rating Tool.[18] The OHAT tool evaluates human research studies on six potential domain-based sources of bias (participant selection, confounding, attrition/exclusion, detection,

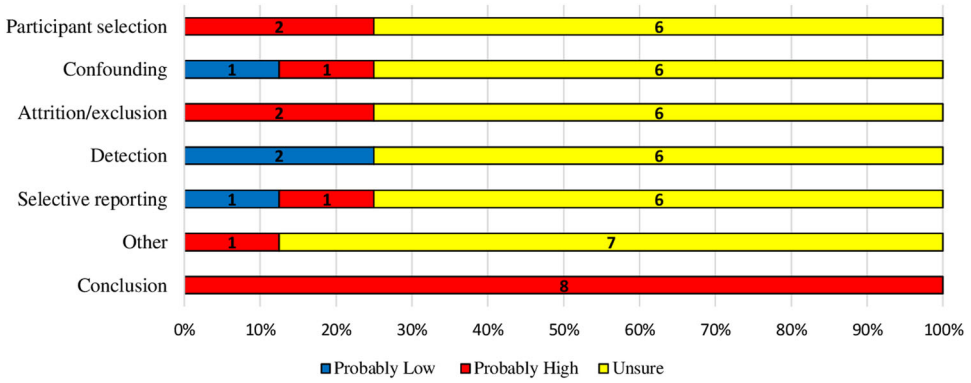

FIGURE 2 Risk of bias scores for included studies, assigned using the Office of Health Assessment and Translation rating tool[18] [Color figure can be viewed at wileyonlinelibrary.com]

selective reporting, and other sources).[19] Risk of bias categories of definitely or probably low, probably high, definitely high, and not applicable were used to rate the risk of bias in each domain. The consensus was achieved between the reviewers by resolving discrepancies through discussion.

2.5 | Data extraction and synthesis of results

Information regarding study characteristics (i.e., study design, location, setting, year, and country), population characteristics (sample size, sex, gender, age at assessment, comorbidities, and asthma medication use), and outcome assessment method (clinical diagnosis and self-reported/questionnaire data) were extracted from individual studies using a pretested data collection form. Asthma medication use at study enrollment was assumed to indicate a provisional diagnosis of asthma. Authors were contacted if important data were missing or unclear. Data were extracted independently by one reviewer (Caseng Zhang) and reviewed for accuracy and completeness by a second reviewer (Anne Hicks). Evidence tables were created in Microsoft Excel™ (Microsoft Corporation) to summarize the characteristics of individual studies.

Data for individual participants were extracted from studies that provided individual patient characteristics and outcomes. The primary outcome of interest was the proportion of participants who stopped or decreased asthma medication after diagnosis or treatment of ILO. The secondary outcome of interest was the proportion of participants who had a change in symptoms after diagnosis or treatment of ILO. Aggregate study data were reported descriptively as the differences between studies did not allow statistical pooling of outcome data. Aggregate study data were weighted to account for the contribution of the different population sizes and subgroups.

A narrative synthesis of the results was conducted due to the heterogeneity in populations, exposures, comparison groups, and outcomes reported. The systematic review without meta-analysis (SWIM) guidelines were used to report data and for evidence synthesis[20] (Table S4.) All identified studies were included in a descriptive summary of participants and outcomes. Effect measures were reported as decrease or cessation of asthma medication use and decrease or resolution of respiratory symptoms. We used the grading of recommendations assessment, development and evaluation (GRADE) framework to assess the certainty of the evidence as high, moderate, low, or very low.[21]

3 | RESULTS

3.1 | Study selection and characteristics of included studies

A total of 1559 references were identified through database searching and 11 additional through reference reviews. After removing duplicates and identifying records from other sources (reference lists of reviews), the titles and abstracts of 1076 studies were screened for relevance, and 31 studies were selected for full-text review for eligibility, resulting in the inclusion of eight cohort studies: one retrospective chart review, one prospective, and six observational cohort studies.[22–29] No randomized controlled trials (RCTs) were identified. Eight case studies were identified but excluded from the analysis. The list of references for excluded studies, along with reasons for exclusion, is available upon request. A detailed description of the included studies is outlined in Table 1. All the studies were conducted at university-affiliated outpatient clinics in the USA; five in an otolaryngology-based setting,[23,25–27,29] one at a pediatric asthma and allergy clinic,[22] one at a pediatric exercise clinic,[24] and one resulted from a health system chart review.[28] Seven of the eight patient populations were selected for suspected or confirmed ILO, while one study[24] evaluated a large cohort of teen athletes with exercise-induced dyspnea where overlapping subsets were diagnosed with ILO and asthma. Age ranged from 7 to 20 years old (the single 20-year-old subject was excluded).[25] Suspected ILO was diagnosed by history or variable obstruction on the spirometry flow volume loop; a diagnosis of ILO was considered confirmed if it was demonstrated with laryngoscopy. Suspected asthma was

TABLE 2 Characteristics of individual patients with a suspected asthma diagnosis before evaluation for ILO from studies reporting individual characteristics

Variable	Study				Merged dataN(%)	Trend
	Doshi et al.[22]	Rameau et al.[25]	Sullivan et al.[26]	Vance et al.[27]		
Primary research question	Long-term outcome of ILO	Long-term outcome of single-visit ILO management	The outcome of SLP treatment for ILO in female adolescent athletes	Characteristics and response to therapy for patients with ILO		
Total study participants	28	22	20	40	110	Primary: PFVM
Met study criteria (%)	23 (82.1)	14 (63.6)	19 (95)	13 (32.5)	69 (62.7)	Secondary: asthma/other
Characteristics of included patients						
Age in years (range) [SD]	13.7 (8–17) [2.7]	13.2 (7–17) [2.8]	14.1 (12–17) [NR]	14.7 (11–17) [1.7]	13.84 [2.49]	Mean 13.8; range 7–17
Male sex (%)	8 (34.8)	5 (35.7)	0 (0)	3 (23.1)	16 (23.2)	Female
Prestudy asthma medication	80% of the entire cohort	11 (78.6)	18 (94.7)	13 (100)	42/46 (91.3)	Almost all prestudy
GERD (%)	NR	5 (35.7)	1 (5)	11 (84.6)	17/46 (40.0)	≅75%
Psychiatric (anxiety or depression) (%)	NR	1 (7.1)	0 (0)	3 (23.1)	4/46 (8.7)	≅50%< 10%
Allergy (%)	NR	9 (64.3)	7 (36.8)	8 (61.5)	24/46 (52.2)	≅ 50%
Other comorbid diagnoses (%)	2 (8.6)	3 (21.4)	1 (5)	8 (61.5)	16/27 (59.3)	≅50%
Symptoms at presentation	23 (100)	14 (100)	19 (100)	13 (100)	69 (100)	Exercise > nonexercise ≅combined symptoms
Exercise only (%)	15 (65.2)	11 (78.6)	14 (73.7)	NR	40/56 (71.4)	
Combined (%)	1 (4.3)	3 (21.4)	5 (26.3)	NR	9/56 (16.1)	
Spontaneous only (%)	7 (30.5)	3 (21.4)	0 (0)	NR	10/56 (17.9)	
Diagnostic modality						
Laryngoscopy	12 (52.2)	14 (100)	0 (0)	10 (76.9)	36 (52.3)	≅50%
Spirometry	1 (4.3)	NR	NR	NR	1/23 (4.3)	<5%
History	10 (43.5)	0 (0)	19 (100)	3 (23.1)	32 (46.4)	≅50%
Response to therapy						SLP is the most common, 80% positive response
SLP and/or behavioral therapy (%)	4/5 (80)	12/14 (85.7)	18/19 (94.7)	7/11 (53.8)	41/49 (83.7)	20% improved with no therapy
Anticholinergic inhaler (%)	4/5 (80)	NR	NR	NR	4/5 (80%)	

(Continues)

TABLE 2 (Continued)

Variable	Study				Merged	Trend
	Doshi et al.[22]	Rameau et al.[25]	Sullivan et al.[26]	Vance et al.[27]	dataN(%)	
No formal therapy (%)	8/14 (57.1)	ND	ND	NR	8/14 (57.1)	
Botox (%)	NR	NR	NR	4/5 (80)	4/5 (80)	
Asthma diagnosis confirmed	4 (17.4)	NR	NR	NR	4 (5.8)	Few studies confirmed asthma
Asthma medication used after the study						>80% decreased or stopped asthma medication
Decreased (%)	23 (100)	0 (0)	4 (21.1)	0 (0)	27 (42.0)	
Stopped (%)	NR	2 (14.3)	15 (78.9)	12 (92.3)	29/46 (63.0)	

Abbreviations: GERD, gastroesophageal reflux disease; ILO, inducible laryngeal obstruction; ND, not done; NR, not reported; PFVM,paradoxical vocal fold motion; SLP, speech-language pathologist.

diagnosed based on study report and/or use of prescribed asthma medication at the time of study enrollment; confirmed asthma diagnosis was by reversible airflow obstruction on spirometry.[22] Study sizes ranged from 35 patients (13 pediatric) in a before/after study[27] to 294 patients in an observational cohort study.[24]

3.2 | Risk of bias

The risk of bias for all included studies was ranked probably high, based on the OHAT criteria assessment (Figure 2). Six studies[22,24,25,27–29] had unclear evaluation results for all six potential domain-based sources of bias (participant selection, confounding, attrition/exclusion, detection, selective reporting, and other sources). In two studies, one showed probably the high risk of bias for all domains except detection (probably low risk)[23]; the other showed probably the low risk of bias for all domains except participant selection and attrition/exclusion (probably high risk).[26] Due to the descriptive nature, small patient numbers, limited recruitment strategies, and reliance on retrospective data with or without a follow-up, all studies had a high risk of bias.

3.3 | Descriptive analysis of participants and outcomes

Four studies provided individual data for a total of 69 patients (Table 2).[22,25–27] The average age at ILO diagnosis was 13.8 years, and 23% were male. Of those formally diagnosed and treated, 80% decreased prescription asthma medication use. Of the 33/69 patients for whom information was available, 52% stopped asthma medication entirely. Comorbidities included laryngopharyngeal and gastroesophageal reflux disease (GERD; 40%) and mental health (anxiety or depression; <10%). Laryngoscopy, the gold standard,[30] was used to confirm ILO in 52% of participants, with 46% receiving a provisional diagnosis based on a history of symptoms alone and 1% flattening of the inspiratory arm of the spirometry flow-volume loop. Counseling associated with provisional diagnosis through history was used as a sole means of ILO management for 22% of patients; 71% received treatment through SLP, and 35% by other means (behavioral therapy and anticholinergic inhalers); 27.5% received more than one treatment.

In the eight included studies, a total of 242 patients (age 7–18 years) with a provisional diagnosis of asthma, based on reported use of asthma medication, and a provisional diagnosis of ILO by clinician assessment were included. After treatment for ILO, 85/135 (62.9%) participants reported respiratory symptoms (dyspnea, cough) resolved and 153/197 (77.7%) reported decreased or discontinued use of asthma medications. Medication and treatment outcomes were not reported for all patients. Of the 54 participants with presumed asthma who did not report an improvement in symptoms after ILO treatment, 36 (16%) continued with the same or increased asthma medication use. The type of asthma medication used (ICS, bronchodilator) was not described for most participants. Medication

TABLE 3 Summarized characteristics of patients with a suspected asthma diagnosis before evaluation for ILO from each of the included studies

	Doshi et al.[22]	Fulton et al.[23]	Hseu et al.[24]	Rameau et al.[25]	Sullivan et al.[26]	Vance et al.[27]	Yibrehu et al.[28]	Ivancic et al.[29]	Trend
Subjects									
Total study participants	28	48	290	22	20	40	18	26	492
Met study criteria (%)	23 (82.1)	31 (65)	86 (29.7)	14 (63.6)	19 (95)	13 (33)	18 (100)	26 (100)	230 (47)
Characteristics of included patients									
Age (range) [SD]	13.7 (8–17) [2.7]	14.5 (10–18) [2.1]	14.6 (NR) [NR]	13.2 (7–17) [2.8]	14.1 (12–17) [NR]	14.7 (11–17) [1.7]	11.6 (NR) [2.3]	14 (11–17) [NR] 4 (15)	≅14.1
Male sex (%)	8 (34.8)	NR[a] (≅ 27)	10 (23)	5 (35.7)	0 (0)	3 (23.1)	4 (22))	26 (100)	F > M (15%)
Prestudy asthma medication	NR,[a] (≅ 80)	31 (100)		11 (78.6)	18 (94.7)	13 (100)	14 (78)		>90% of reported
Allergy (%)	NR	NR[a] (46)	NR[a] (2)	8 (62)	7 (37)	8 (62)	4 (22)	12 (46)	~40% of reported
GERD (%)	NR	NR[a] (4)	NR[a] (15)	5 (36)	1 (5)	11 (85)	8 (44)	3 (12)	~30% of reported
Psychiatric (anxiety/depression) (%)	NR	NR	NR[a] (6)	1 (7)	1 (5)	3 (23)	6 (33)	6 (23)	~20% of reported
Other (%)	2 (8.6)	NR	NR	3 (21)	1 (5)	8 (61)	NR	1 (4)	~20% of reported
Any PFVM symptoms at presentation	23 (100)	NR (≅ 98)	NR	14 (100)	19 (100)	13 (100)	NR	NR	>50% EILO < 50% combined, spontaneous rare, but limited reporting
Exercise only (%)	15 (65.2)	NR	NR	11 (78.6)	14 (73.7)	NR	18 (100)	13 (50)	
Combined (%)	1 (4.3)	NR	86 (100)	3 (21.4)	5 (26.3)	NR	NR	10 (38)	
Spontaneous only (%)	7 (30.5)	NR	NR	3 (21.4)	0 (0)	NR	NR	3 (12)	
Diagnostic modality									
Laryngoscopy	12 (52.2)	31 (100)	86 (100)	14 (100)	0 (0)	10 (76.9)	NR	26 (100)	85% of reported
Spirometry	1 (4.3)	NR	NR	NR	NR	NR	NR	NR	<5% of one study
History	10 (43.5)	0 (0)	NR	0 (0)	19 (100)	3 (23.1)	NR	0 (0)	15% of reported
Treatment									
SLP and/or behavioral (%)	4/5 (80)	NR[a] (100)	86/86 (100)	12/14 (85.7)	18/19 (94.7)	7/11 (53.8)	14/16 (88)	14/21 (67)	>75% responded
Ipratropium bromide (%)	4/5 (80)	NR	40 (47)	NR	NR	NR	1/10 (10)	NR	~10% responded
No formal therapy (%)	8/14 (57.1)	NR	0 (0)	ND	ND	NR	1/2 (50)	3/5 (60)	~30% responded

(Continues)

TABLE 3 (Continued)

	Doshi et al.[22]	Fulton et al.[23]	Hseu et al.[24]	Rameau et al.[25]	Sullivan et al.[26]	Vance et al.[27]	Yibrehu et al.[28]	Ivancic et al.[29]	Trend
Botox (%)	NR	NR	NR	NR	NR	4/5 (80)	NR	NR	~80% responded
Asthma medication after study									
Decreased (%)	23 (100)	NR	NR	2 (14.3)	4 (21.1)	0 (0)	NR	17 (65)	~65% of reported
Stopped (%)	NR	NR	NR	2 (14.3)	15 (78.9)	12 (92.3)	NR	NR	~75% of reported

Abbreviations: EILO, exercise-induced laryngeal obstruction; F, female; GERD, gastroesophageal reflux disease; ILO, inducible laryngeal obstruction; M, male; ND, not done; NR, not reported; PFVM,paradoxical vocal fold motion; SLP, speech-language pathologist.

[a]Proportions reported for the entire cohort, not limited cohort included in the study, therefore are approximate.

and treatment outcomes for the remaining 18 subjects were not reported. Of patients with presumed ILO, 86.8% were confirmed by laryngoscopy (Table 3); (179/212 from seven studies where laryngoscopy was reported), few studies reported confirmation of asthma diagnosis through spirometry (23/23 in one study; limited and variable reporting in other studies).

The GRADE method was used to summarize the evidence for interventions (Table 4).[21] There is moderate certainty of evidence that SLP and/or behavioral therapy provide improvement in symptoms,[22–29] and a very low certainty of evidence supporting an anticholinergic inhaler[22,24] or Botox therapy[27] to improve symptoms. The certainty of the evidence for decreasing or stopping asthma medications was very low for any intervention, however in the context of few reported outcomes.[22,25–27,29]

4 | DISCUSSION

4.1 | Key findings

This systematic review of the impact of identification and treatment of obstructive laryngeal disorders on asthma medication use in pediatric patients with symptoms of both ILO and asthma identified eight descriptive studies of children with a provisional diagnosis of both conditions. Of 242 patients in these studies, few reported persistent symptoms or used asthma medication after ILO diagnosis and treatment, although most were assumed to have asthma before ILO diagnosis. This is in keeping with a study of 66 adults with ILO, 79% of whom decreased asthma medication after diagnosis.[10]

Guidelines for severe asthma management include identification and treatment of comorbidities and alternate diagnoses, including obstructive laryngeal disorders.[31–33] In this review, just over 20% of patients with suspected ILO had a confirmed diagnosis of asthma.[22,24] These numbers are unlikely to reflect trends in a population with suspected asthma since the studies were all drawn from ILO or exercise clinics. A 2015 evaluation of 99 adolescents with exercise-induced symptoms in Sweden similarly diagnosed 19.2% with asthma; 5.7% of their patients received an EILO diagnosis with 4.8% demonstrating overlap.[9] This suggests that ILO may be underdiagnosed in the adolescent population. In this study, patients with a provisional ILO diagnosis demonstrated higher rates of decreasing or stopping asthma medication than those with a formal diagnosis, but mainly in the context of refusing treatment, similar to adult findings.[10] Table 5 provides a summary of common clinical differences between ILO phenotypes and asthma. Visual confirmation of ILO is important to rule out physiologic problems including VF paralysis, paresis, or stenosis.[13] Functional and psychogenic diagnoses including hyperventilation, which may be triggered by exercise and can be associated with anxiety and panic attacks, also should be considered.[34,35]

Several studies reported comorbidity including GERD. Laryngopharyngeal reflux may increase laryngeal inflammation, and ILO pathophysiology may contribute to GERD symptoms in some

TABLE 4 Summary of findings with the certainty of evidence (GRADE)[21]

Outcome	Effect	Number of participants (number of studies)	Certainty of evidence (GRADE)
The study used laryngoscopy for diagnosis	Most participants	179/212 (7)	NA
Spirometry confirmed asthma diagnosis	Few participants	23/23 (1); limited in others	NA
Symptoms improved			
SLP and/or behavioral therapy	Almost all improved symptoms	193/230 (8)	Moderate
Anticholinergic inhaler	Some improved symptoms, limited reporting	5/15 (2); 40/86 outcome NR	Very low
Botox	Rare, some improved symptoms	4/5 (1)	Very low
No defined therapy	About 50% improved symptoms	12/21 (4)	Very low
Asthma medications decreased or stopped			
SLP and/or behavioral therapy	Some selected patients	11/38 (5)	Very low
Anticholinergic inhaler	Some selected patients	4/5 (1); 50/104 outcome NR	Very low
Botox	Rare, good in selected patients	4/5 (1)	Very low
No defined therapy	Rare, mainly patients who refused therapy	18/18 (4)	Very low
Comorbidities with similar symptoms			
Allergy	Relatively common	18/68 (3)	Low
GERD	Relatively common	18/59 (3)	Low
Psychiatric (anxiety, depression)	Relatively common	17/68 (3)	Low
Deconditioning	10% of exertional dyspnea no asthma or ILO	29/290 (1)	Very low
Other	Various non-respiratory conditions	14/69 (4)	Very low

Abbreviations: GERD, gastroesophageal reflux disease; GRADE, grading of recommendations assessment, development and evaluation; ILO, inducible laryngeal obstruction; NA, not applicable; NR, not reported; SLP, speech-language pathologist.

TABLE 5 Comparison of typical clinical presentation of asthma and ILO subtypes[22]

	SILO	EILO	Asthma
Trigger	None	Exercise	Variable, multiple
Signs			
Sound	Stridor (typically inspiratory)	Stridor (typically inspiratory)	Wheeze (typically expiratory)
Location	Extrathoracic	Extrathoracic	Intrathoracic
Symptoms			
Onset	Sudden	Sudden	Variable
Length	Minutes to hours	Minutes to hours	Can be prolonged
Resolution	Self-resolving or breathing exercises	Self-resolving or breathing exercises	May require medication
Beta-2 agonist response	No	No	Yes

Abbreviations: EILO, exercise-induced laryngeal obstruction; ILO, inducible laryngeal obstruction; SILO, spontaneous-induced laryngeal obstruction.

patients.[30] The proposed mechanism is through increased negative intrathoracic pressure generated during work of breathing with ILO overcoming esophageal opening pressure.[36] In patients diagnosed with anxiety, 94.7% reported symptom resolution after ILO treatment. Acute ILO episodes can include chest tightness, choking, dyspnea, dysphagia, and globus sensation.[37] Reducing the frequency and severity of ILO episodes may have addressed anxiety.

4.2 | Limitations

All the studies focused on ILO, not asthma, introducing selection bias. Although ILO is likely underdiagnosed, the proportion of asthma patients with ILO cannot be predicted from these data. The review process focused specifically on both asthma and ILO and may have failed to identify studies that did not describe both in the abstract. The studies were heterogeneous, all had a high risk of bias, and 7/8 were small. Even by combining descriptive data, there was inadequate power to do more than demonstrate trends.

5 | CONCLUSION

When should pediatric patients with presumed asthma be evaluated for laryngeal obstruction syndromes? This is a challenging question that cannot be answered with the current evidence. In this review, there was an approximate 20% overlap with asthma in ILO patients, but it was not possible to estimate the proportion of asthma patients with ILO. Comorbidities, or alternative physiologic and psychogenic diagnoses, also need to be considered.[13,34] Investigation for ILO is recommended for patients with severe asthma.[31] In this review, SLP was effective for both ILO phenotypes: EILO and SILO, and there was limited evidence for treating EILO with inhaled ipratropium bromide. Further research, particularly evaluating asthma patients for laryngeal obstruction syndromes as well as comorbidities, is required. A comprehensive review could be completed at the health systems or individual clinic level to ascertain frequencies of presentation, although it would have significant limitations. A prospective cohort study of patients presenting with suspected asthma could provide more accurate information. An RCT would better assess diagnostic and therapeutic options; given the nature of laryngoscopy and speech-language pathology, it could not be blinded but would still provide high-quality information needed to inform clinical care.

AUTHOR CONTRIBUTIONS

Caseng Zhang: Conceptualization (equal); data curation (equal); formal analysis (equal); methodology (equal); project administration (equal); writing – original draft (equal); and writing – review and editing (equal). **Maria B. Ospina**: Conceptualization (supporting); methodology (equal); writing – original draft (supporting); and writing – review and editing (supporting). **Vishnu Martha**: Data curation (supporting); validation (supporting); and writing – review and editing (supporting). **Ghiath Alnouri**: Data curation (supporting); validation (supporting); and writing – review and editing (supporting). **Liz Dennett**: Conceptualization (supporting); data curation (supporting); investigation (equal); methodology (supporting); resources (supporting); writing – original draft (supporting); and writing – review and editing (supporting). **Robert Sataloff**: Investigation (supporting); resources (supporting); supervision (supporting); and writing – review and editing (supporting). **Anne Hicks**: Conceptualization (lead); data curation (equal); methodology (equal); supervision (lead); validation (equal); writing – original draft (equal); and writing – review and editing (lead).

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Anne Hicks http://orcid.org/0000-0001-6553-3826

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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