Influence of Inhaled Corticosteroids on Voice Quality: A Systematic Review☆

*,†,‡,§Jérôme R. Lechien *Mons, †Baudour, Belgium, and ‡§Paris, France

Summary: Objective. To investigate the incidence of dysphonia and the related voice quality assessment impairment in patients treated with inhaled corticosteroids.

Methods. A laryngologist and librarian conducted a PubMED, Scopus, and Cochrane Library systematic review related to the voice quality features in patients treated with inhaled corticosteroids through the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.

Results. Of the 366 identified studies, 21 publications met inclusion criteria (15 026 subjects). Dysphonia prevalence ranged from 3.0% to 34.0% according to patients and 53.3%-89.0% according to practitioners. Subjective, laryngostroboscopic, and objective voice evaluations (aerodynamic and acoustic) showed impairments influenced by IC doses, treatment duration, and particle sizes. Mean MINORS score was 5.8 ± 2.1. Substantial heterogeneity existed across studies regarding IC drugs, inclusion/exclusion criteria, and outcomes. There was no study considering a multidimensional voice quality evaluation. Most studies failed to address key confounding factors, including laryngopharyngeal reflux disease, tobacco consumption, and active allergic rhinitis.

Conclusion. Inhaled corticosteroids significantly impact voice quality, with substantial discrepancy between patient-reported and clinician-reported dysphonia rates. The drug features influence the occurrence of dysphonia, despite methodological limitations. Future research requires standardized multidimensional voice quality assessments and better control of confounding factors to clarify the underlying pathophysiological mechanisms.

Key Words: Laryngeal—Otolaryngology—Otorhinolaryngology—Voice—Corticosteroids—Inhaled—Vocal fold—Outcomes.

INTRODUCTION

Inhaled corticosteroids (IC) are one of the most used drugs in Europe and the United States of America for the treatment of asthma and chronic obstructive pulmonary disease (COPD).[1] To date, an estimated 300 million people worldwide currently suffer from asthma, and an additional > 100 million persons are likely to suffer from this disease by the year 2025,[2] leading to a substantial burden on society in morbidity, quality of life, and healthcare costs.[3] IC are potentially associated with systemic and local adverse events in up to 81.5% of cases,[4] with a dose- and use-dependence according to meta-analyses.[5] Voice quality disorders may affect 5%-58% of the patients.[4,6] The exact mechanisms underlying the development of dysphonia in these patients remain poorly investigated, and the origins of dysphonia may have multiple confounding factors.[6]

The present review aims to investigate the incidence of dysphonia and related voice quality assessment impairments in patients treated with ICs.

MATERIALS AND METHODS

The criteria for publication inclusion and exclusion have been based on the population, intervention, comparison, outcome, timing, and setting framework.[7] Two independent investigators conducted the literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for systematic reviews.[8]

Patient population

Prospective, retrospective, controlled, uncontrolled, or randomized clinical studies published from January 1985 to January 2025 were considered. Studies were published in English peer-reviewed journals and reported data for more than 10 adult individuals. The inclusion criteria, specifically the disease of included patients (eg, asthma, COPD) under ICs, had to be specified in studies. The criteria used for the asthma or COPD diagnosis were collected. There were no exclusion criteria based on age, ethnicity, socioeconomic status, and comorbidities. Data from population-based registries, cross-sectional surveys, or clinical hospital studies were considered. Case reports, pediatric, and animal model studies were excluded.

Intervention and comparison

The investigators considered studies assessing the occurrence of voice quality disorders in patients treated with IC.

Accepted for publication April 10, 2025.
☆ This research received no external funding.

From the *Department of Surgery, UMONS Research Institute for Health Sciences and Technology, University of Mons (UMons), Mons, Belgium; †Division of Laryngology and Bronchoesophagology, Department of Otolaryngology Head Neck Surgery, EpiCURA Hospital, Baudour, Belgium; ‡Department of Otolaryngology-Head and Neck Surgery, Foch Hospital, School of Medicine, UFR Simone Veil, Université Versailles Saint-Quentin-en-Yvelines (Paris Saclay University), Paris, France; and the §Department of Otolaryngology, Elsan Hospital, Paris, France.

Address correspondence and reprint requests to: Jérôme R. Lechien, Chair and Professor of Surgery, University of Mons, Mons, Belgium. E-mail: Jerome.Lechien@umons.ac.be

Journal of Voice, Vol xx, No xx, pp. xxx–xxx
0892-1997

https://doi.org/10.1016/j.jvoice.2025.04.008

Controlled studies comparing several groups according to the doses, the molecules, or other therapeutic findings were considered.

Outcomes

The demographic and study outcomes were collected, ie, study design, number of patients, gender ratio, and age (mean/median). The primary outcomes included the patient's disease, stage, IC drugs, doses, voice quality outcomes, and results. The secondary outcomes included the prevalence of dysphonia, definition and methods of voice quality outcome measurements, potential other IC adverse events, and substantial comorbidities that could affect the outcome investigation (eg, allergy, occupational factors, tobacco consumption, laryngopharyngeal reflux disease, and other respiratory comorbidities).

Timing and setting

There were no criteria for specific stages or timing in the "disease process" of the study population.

Search strategy

The author and a trained librarian conducted the literature search on PubMED, Scopus, and Cochrane databases. The databases were screened for abstracts and titles referring to the description of IC-related voice quality disorders in adults. The following keywords were associated with AND/OR in databases: "voice," "ICs," "dysphonia," "adverse event," "vocal fold," "incidence," "prevalence," "acoustic," "aerodynamic," "asthma," and "COPD." The two investigators analyzed the full texts of the selected publications. The results of the search strategy were reviewed for relevance, and the reference lists of the selected publications were examined for additional pertinent studies. Potential discrepancies in extracted and synthesized data were discussed and resolved by the investigators. The type of study was classified according to the levels of evidence (I-V).[9]

Bias analysis

The bias analysis was performed with the Methodological Index for Non-Randomized Studies (MINORS) tool, which is a validated instrument designed for assessing the quality of non-randomized surgical studies.[10] The MINORS includes 12 items for the analysis of methodological points of comparative and noncomparative studies. The items were scored 0 if absent, 1 when reported but inadequate, and 2 when reported and adequate. The aim of the study was rated as clearly stated (2), unclear (1), or absent (0). The inclusion of patients was rated as optimal (2) for clearly stated consecutive patients, suboptimal for unclearly stated consecutive patients (1), or absent mention of consecutive inclusion pattern (0). The prospective data collection was rated as prospective (2), retrospective analysis of prospectively recruited patients (1), or absent (0). The quality of endpoints was considered as high (2) if the authors assessed the voice quality with validated subjective and objective voice quality outcomes.[11] The voice quality evaluation with subjective or objective approach was considered as suboptimal (1), while the lack of use of validated subjective or objective outcomes was considered as low (0). The follow-up period outcome consisted of the time between the start of the IC and the voice quality evaluation. It was considered as adequate (2) for at least 6 months of treatment. A shorter follow-up was considered as less reliable to evaluate accurately the potential effect of IC on voice quality (0). Finally, a 5% rate of lost-to-follow-up patients was considered as the threshold in the MINORS, while the study size prospective calculation needed to be carried out (2), mentioned as unnecessary (1), or absent (0). The ideal MINORS score was 16 for non-comparative studies and 24 for comparative studies.[10]

RESULTS

Of the 366 identified studies, 21 publications[12–32] met the inclusion criteria (Figure 1). There were seven prospective uncontrolled,[15,16,18–20,22,32] five prospective controlled,[13,21,23,29,30] five cross-sectional,[17,24,25,28,31] and four retrospective[12,14,26,27] studies (Table 1). The present systematic review reports findings of 15 026 subjects. Some studies reported the primary diagnosis of included patients, while others just mentioned having included IC users (Table 2). The data of 6722 healthy controls have been included. There were 8646 females and 6337 males. Gender was not specified in one study.[22] The mean age ranged from 20.7 to 58.9 years (Table 2). The demographic and drug data are reported in Table 2. Budesonide and beclomethasone dipropionate were the most used drugs across studies. Eight studies reported findings of patients treated with a single IC therapy,[18–20,22,27,29–31] while in 10 studies,[12–17,25,26,28,32] there was a myriad of several IC therapies pooled into one cohort of patients. The IC was unspecified in three studies.[21,23,24]

Voice quality outcomes

The key findings of voice quality outcomes are summarized in Table 3. Both subjective and objective voice quality outcomes have been used to investigate the voice changes from pre- to post-IC treatments or the voice quality differences between IC users versus occasional or nonusers (considered as healthy individuals). Among subjective evaluations, most outcomes consisted of unvalidated patient- or practitioner-reported dysphonia or voice disorders. The patient-reported dysphonia prevalence ranged from 3.0% to 34.0% of cases,[15,17,28,31] with potential dose- and IC use duration effects.[24,25] Patients typically reported hoarseness and voice intensity reduction (11.5% to 16.0%), while the Voice Handicap Index was used in only one study.[20] The prevalence of practitioner-reported dysphonia ranged from 53.3% to 89.0% of cases,[16,26] with an IC use duration effect.[13] GRBAS was used in three studies, which demonstrated moderate impairments of grade of dysphonia, roughness and breathiness, and significantly higher

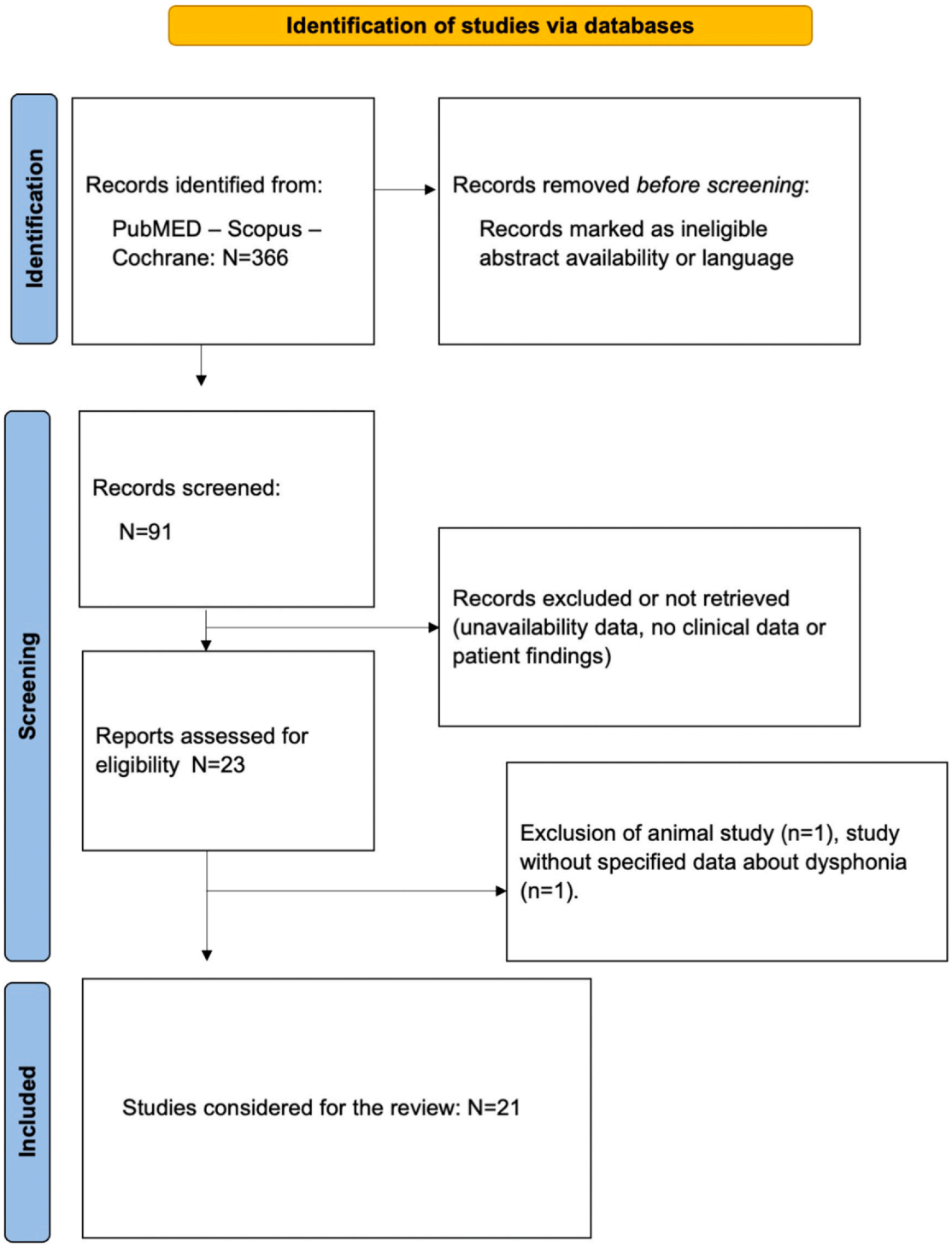

FIGURE 1. PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

scores in long-time IC users compared with new users (Table 3).[13,19,22] Only one study reported conflicting data with no association between the use of IC and the voice subjective scale.[22]

Laryngostroboscopy has been used in six studies.[13,14,16,19,26,27] Studies commonly showed that IC users had a substantial number of stroboscopic abnormalities, with IC use duration[13] and particle size[14] effects. Thus, the particle size influenced the videolaryngostroboscopy (VLS) examination with significantly higher abnormalities in patients using standard particles versus those using small particles.[14] In a comparative study, Krishnan et al reported a significantly higher number of VLS abnormalities in > 6-month IC users compared with new users, including asymmetrical mucosal wave, reduced amplitude and frequency, absent mucosal wave, incomplete glottic closure, and non-periodic vibration.[13] In terms

TABLE 1.
Demographics

References	Design	*N*	F/M	Age	Drugs	Voice Outcomes	Results
Naunheim et al 2022[12]	Retrospective	*n* = 6551 asthma	3734/2817	58.9	Budesonide (22%)	OTO dysphonia	Asthma > CT
	Case-control	*n* = 6551 CT	3734/2817	57.0	Fluticasone (75%)		
Krishnan et al 2022[13]	Prospective	Gr1 = 98 > 6 months use IC	35/63	53.7	Fluticasone + salmeterol 20.4% (*n* = 20)	VLS abnormalities	Gr1 > Gr2
	Controlled	Gr2 = 98 CT new IC users	35/63	34.7	Budesonide + formoterol 79.6% (*n* = 78)	GRBAS	Gr1 > Gr2
		Moderate-to-severe asthma				OTO dysphonia (%)	Gr1 = 62.2%, Gr2 = 27.6%
Vance et al 2019[14]	Retrospective	*n* = 40 asthma			Ciclesonide and beclomethasone dipropionate	VLS abnormalities	Gr2 > Gr1
		Gr1 = 20 small particles	15/5	44.2*			
		Gr2 = 20 standard particles	15/5	46.0*	Budesonide + formoterol and fluticasone		
Hong et al 2019[15]	Prospective	*n* = 101		39.0*	Fluticasone propionate (250 μg) and budesonide (400 μg)	PAT dysphonia (Gr1-2)	5/68 (7.4%)-1/33 (3.0%)
	Uncontrolled	Gr1 = 68 UACS	43/25	37.0*			
		Gr2 = 33 UCC	23/10	47.0*			
Hassen et al 2015[16]	Prospective	*n* = 30 asthma	15/15	21.3 (F)	Beclomethasone dipropionate (400 μg)	2 OTO dysphonia	53.3%
	Uncontrolled			20.7 (M)	Budesonide (200 to 400 μg)	VFE, IAT, VFO, and VFA	56.7%-56.7%—5.3%-5.5%
						LPRD signs	36.7%
						F0	normal values > IC users
						Jitter %, Shimmer %	ICS users > normal values
						NHR, SPI, and PFR	ICS users > normal values
Pinto et al 2013[17]	Cross-sectional	*n* = 200 asthma	159/41	50.7	Budesonide (*N* = 171)	PAT hoarseness/LOV	26%-5.5%
					Beclomethasone (*N* = 6) Budesonide + beclomethasone (*N* = 23)	Reduced vocal intensity	11.5%
Sahrawat et al 2013[18]	Prospective	*n* = 30 healthy adults	15/15	24.0	Fluticasone propionate (500 μg)	F1	Post > pre
	Uncontrolled					1st, 2nd bandwidth, F0, and F2	Pre = post—6 days
						FSP, ST	Pre > post—6 days

TABLE 1 (*Continued*)

References	Design	*N*	F/M	Age	Drugs	Voice Outcomes	Results
Kim et al 2011[19]	Prospective	*n* = 29 IC users	19/10	46.0 (M)	Budesonide and formoterol (160/4,5 μg)	VLS abnormalities	Post > pre
	Uncontrolled			33.4 (F)		GRBAS	Post > pre (*n* = 4)-post = pre (*n* = 25)
						F0, AMPQ, and CQD	Pre = post
Erickson and Sivasankar 2010[20]	Prospective	*n* = 14 IC users without	9/5	23.1	Fluticasone propionate and	VHI	All < 33.7
	Uncontrolled	SLP dysphonia			salmeterol (250/50 μg)	PTP	Post—2 hours > pre
Bhalla et al 2008[21]	Prospective Controlled	Gr1 = 46 asthma Gr2 = 4 healthy individuals	24/26	59.0*	Unspecified IC	OTO-voice weakness Pharyngitis hoarseness	Asthma > CT + correlated
Stanton et al 2008[22]	Prospective Uncontrolled	*n* = 43 asthma	NA	NA	Beclomethasone dipropionate	VoiSS-IC association GRBAS	Not significant 13/43 patients: ⩾1 abnormal score
Bhalla et al 2009[23]	Prospective	*n* = 46—Gr1 = IC users, Gr2 =	24/22	46.0*	Unspecified IC	Jitter%, Shimmer%, and CQD	Gr1 > Gr2-3
	Controlled	occasional IC users, and Gr3=CT					
Bhalla et al 2008[24]	Cross-sectional	*n* = 144 IC users	81/63	53.4	Unspecified IC	PAT weak voice	Long IC users > short IC users
						PAT hoarseness	Long IC users > short IC users
Foster et al 2006[25]	Cross-sectional	*n* = 228 IC users—27 CT	143/112	42.0*	Beclomethasone dipropionate	PAT dysphonia	Gr3 > Gr2 > Gr1 > CT
		Gr1,2,3 = low, mid, and high IC doses			Budesonide- fluticasone propionate		
Gallivan et al 2007[26]	Retrospective	*n* = 38 IC users with dysphonia	28/9	56.9	Fluticasone propionate + salmeterol	OTO dysphonia (%)	89%
					Fluticasone propionate-budesonide	VLS abnormal MWSP-MWAM	76%-63%-50%-35%
					Triamcinolone acetonide Beclomethasone dipropionate	Phase/glottic closure	74%-63%-63%-59%
Mirza et al 2004[27]	Retrospective	*n* = 9 IC users with	6/3	49.9	Fluticasone and salmeterol	VLS abnormalities—Leuko	*n* = 8/9-7/9
		dysphonia			(100, 250, or 500 μg/50 μg)	VLS hyperemia—GERD	*n* = 8/9-9/9

TABLE 1 (*Continued*)

References	Design	*N*	F/M	Age	Drugs	Voice Outcomes	Results
Ihre et al 2004[28]	Cross-sectional	*n* = 280 asthma	192/82	47.0 (F)	Budesonide	PAT dysphonia—IC use	+ association
				48.0 (M)	Fluticasone- beclomethasone	PAT hoarseness	24.5%
Balter et al 2001[29]	Prospective	Gr1 = 77 asthma daily IC	49/28	33.3	Beclomethasone dipropionate (250 μg)	BDT—Jitter %	+ association
	Randomized	Gr2 = 10 CT occasional BDT	7/3			Jitter	Pre = post
	Controlled					Shimmer %	Gr2: pre = post, Gr1: pre > post
Crompton et al 2000[30]	Prospective	*n* = 51 asthma	39/12	57.0	Budesonide 200 μg	F0	Gr2: post = pre, Gr1: pre = post
	Randomized	*Gr1 = 26 Nebuhaler*	*21/5*	58.0		Jitter%, MPT, PQ, and semitone	Gr2: pre = post, Gr2: pre = post
	Controlled	*Gr2 = 25 Turbuhaler*	*18/7*			Dysphonia questionnaire	Gr1-2 pre = post
Williamson et al 1995[31]	Cross-sectional	Gr1 = 255 IC users	154/101	54.0	Unspecified BDP (*n* = 189)	PAT dysphonia	Gr1 > Gr2-3
		Gr2 = 100 CT	42/58	51.0	Budesonide	Hoarseness	Gr1 = 86 (34%)
						Reduced intensity	Gr1 = 40 (16%)
Watkin and Ewanowski 1985[32]	Prospective	*n* = 11 asthma	6/5	55.2 (F)	Triamcinolone acetonide		F0, MPT, and oral air velocity
	Uncontrolled			54.4 (M)	Beclomethasone dipropionate	Triamcinolone acetonide	Impairment after 1, 2y
						Beclomethasone dipropionate	No change

* Median. *Abbreviations:* AMPQ, amplitude quotient distribution; BDT, bronchodilator therapy; COPD, chronic obstructive pulmonary disease; CQD, closed quotient distribution; CT, controls; FSP, mean first spectral peak; GERD, gastroesophageal reflux disease; IAT, interarytenoid thickening; IC, inhaled corticosteroids; Leuko, leukoplakia; LOV, loss of voice; LPRD, laryngopharyngeal reflux disease; mo, month(s); MWAM, mucosal wave amplitude/magnitude; MWSP, mucosal wave symmetry/periodicity; NHR, noise-to- harmonic ratio; OTO/SLP dysphonia, dysphonia subjectively diagnosed by otolaryngologist/speech language pathologist; PAT dysphonia, patient-reported dysphonia; PFR, phonatory frequency range; PQ, phonation quotient; PTP, phonation threshold pressure; SPI, soft phonation index; ST, spectral tilt; UACS, upper airway cough syndrome; UCC, unexplained chronic cough; VFA, vocal fold atrophy; VFE, vocal fold erythema; VFO, vocal fold edema; VLS, videolaryngostroboscopy; VoiSS, voice symptom score.

TABLE 2.
General Outcomes

Outcomes	*N*	%
Patients (n, %)	15 026	100
Asthma—IC users	7440	49.5
Other conditions—IC users	864	5.8
Healthy controls	6722	44.7
Gender		
Females (*n*, %)	8646	57.5
Males (*n*, %)	6337	42.2
Unspecified gender (*n*, %)	43	0.3
Age		
Mean age (range, years)	20.7-58.9	-
Median age (range, years)	37.0-59.0	-
Drugs	*N*	*References*
Budesonide	10	12,15-18,25,26,28,30,31
Fluticasone	5	12,15,25,26,28
Fluticasone + salmeterol	4	13,20,26,27
Budesonide + formoterol	2	13,19
Ciclesonide and beclomethasone dipropionate	1	14
Budesonide + formoterol and fluticasone	1	14
Beclomethasone dipropionate	8	16,17,22,25,26,28,29,32
Budesonide + beclomethasone	1	17
Unspecified IC	3	21,23,24
Triamcinolone acetonide	2	26,32
Unspecified bronchodilators	1	31

Abbreviations: IC, inhaled corticosteroids; *N*, number.

of abnormalities, Gallivan et al reported abnormal mucosal wave symmetry/periodicity in 63%-76% of IC users with self-reported dysphonia, and abnormal mucosal wave amplitude/magnitude in 35%-50% of cases. Phase and glottic closure abnormalities occurred in 63% to 74%, and 59% to 63% of cases, respectively.[26] Hassen and Hasseba reported in 30 asthma patients the following VLS abnormalities: vocal fold erythema (56.7%), interarytenoid thickening (56.7%), vocal fold edema (5.3%), and vocal fold atrophy (5.5%).[16] Among vocal fold abnormalities, leukoplakia was reported in 7/9 IC user patients with a complaint of dysphonia in the study of Mirza et al. who additionally supported a potential high prevalence of reflux disease in these patients.[27]

The voice quality of IC users was objectively assessed with acoustic measurements and aerodynamics in 8[16,18,19,22,23,29,30,32] and three studies, respectively.[20,30,32] Percent jitter and percent shimmer reported elevated values in IC users with a dose effect.[16,23,29] Three studies suggested abnormal values of noise-to-harmonic ratio, soft palate index, or some spectral outcomes.[16,18,19] Controversial results were found regarding the potential influence of ICs on the F0,[16,19,30,32] phonation threshold pressure or quotient,[20,30] and maximum phonation time.[30,32]

Bias analysis and confounding factors

There was a substantial heterogeneity across the study for inclusion and exclusion criteria. The literature analysis for confounding factors revealed partial information about reflux, smokers, and allergic patients. Reflux information was not reported in 11[12,14–18,25,29–32] studies. In the others, the prevalence of gastroesophageal reflux disease/laryngopharyngeal reflux disease symptoms ranged from 26% to 52.6%,[22,26,28] while some authors have carefully excluded patients with reflux symptoms and/or findings.[13,19–21,23,24] Similar heterogeneity was found for tobacco without information in nine studies.[12,14–16,22,27,29,30,32] In others, the proportion of smokers or former smokers ranged from 13% to 44.5%.[17,25,26,28,31] Allergy, especially allergic rhinitis, details were provided in six studies,[15,20,21,23,24,28] with only two studies reporting the prevalence of allergic patients (42.6% and 55%).[15,28]

Table 4 reported the bias analysis details (MINORS). The mean MINORS is 5.8 ± 2.1. The low MINORS score is related to the predominance of cross-sectional, retrospective, and survey-based studies, highlighting the limited number of prospective studies assessing multidimensional voice quality. Indeed, there was no study using both validated and standardized patient-reported outcome questionnaires and perceptual evaluations combined with acoustic and aerodynamic measurements. Concerning follow-up, the longitudinal studies reported a wide range of durations, including 2 hours,[20] 6 days,[18] 12 weeks,[19,30] 16 weeks,[29] and 1 to 2 years.[32] There was no formal study size calculation in prospective studies, while the rate of lost-to-follow-up was adequate in only four studies.[13,20,23,24]

TABLE 3.
Voice Quality Outcomes

	Results			
Outcomes	Primary	References	Controversial	References
Subjective voice quality				
Patient-reported dysphonia	Variable prevalence: 3.0% to 34.0%	[15,17,28,31]	No VoiSS-IC use association	[22]
	Long-time > short-time users	[24]	-	
	Dose-dependance	[25]	-	
Patient-reported reduced voice intensity	Moderate prevalence in IC users (11.5%-16.0%)	[17,31]	-	
	Long-time > short-time users	[24]	-	
Voice Handicap Index	Not impaired in IC users	[20]	-	
Perceptual evaluations			*Blinded evaluations*	
Otolaryngologist-reported dysphonia	Asthma/IC users > controls	[12]	No	
	Variable prevalence: 53.3%-89.0%	[16,26]	No	
GRBAS	Long-time > short-time users	[13]	No	
	Moderately impaired in IC users	[19,22]	No	
Otolaryngologist-reported voice weakness	Asthma/IC users > controls	[21]	No	
VLS abnormalities	Significant abnormalities in IC users	[16,19,26,27]	-	
	Long-time > short-time users	[13]	-	
	Standard > small particles	[14]	-	
Objective voice quality			*Controversial*	
Acoustics				
F0	Abnormal values in IC users	[16,32]	No change related to IC use	[19,30]
Jitter %	Abnormal values in IC users	[16,23]	No change related to IC use	[30]
	Dose-dependance	[23,29]	-	
Shimmer %	Abnormal values in IC users	[16,23,29]	-	
	Dose-dependance	[23,29]	-	
Noise-to-harmonic ratio	Abnormal values in IC users	[16]	-	
Soft palate index	Abnormal values in IC users	[16]	-	
Formants	Potentially impaired values in IC users	[18]	-	
Mean first spectral peak	Potentially impaired values in IC users	[18]	-	
Spectral tilt	Potentially impaired values in IC users	[18]	-	
Amplitude quotient distribution	No impact of IC	[19]	-	
Closed quotient distribution	Impaired in IC users	[22]	No impact of IC	[19]
	Dose-dependance	[22]	-	
Aerodynamics				
Phonation threshold pressure/ quotient	Impaired 2-hour post-IC use	[20]	No change related to IC use	[30]
Maximum phonation time	Impaired in IC users	[32]	No change related to IC use	[30]

Abbreviations: IC, inhaled corticosteroids; GRBAS, grade of dysphonia, roughness, breathiness, asthenia, strain; VLS, videolaryngostroboscopy; VoiSS, Voice Subjective Scale.

DISCUSSION

Laryngologists commonly encounter patients with IC therapy and dysphonia. This systematic review supported the clinical relationship between IC use and the development of dysphonia, as well as impairments in aerodynamic and acoustic measurements. However, the exact prevalence of dysphonia in IC users remains unknown. The patient-reported dysphonia rate appears substantially lower than the practitioner-reported dysphonia, while many studies demonstrated the influence of IC intrinsic factors, including doses, types of particles, and duration of treatment.[13,14,22–25,29]

The pathophysiological mechanisms underlying these observations are still unknown. Interestingly, the association between particle size and the occurrence of dysphonia could be explained by the respiratory tract deposition of small particles lower than the larynx. The particle sizes of

TABLE 4.
Bias Analysis

References	Clearly Stated Aim	Consecutive Patients	Prospective Data Collection	Endpoints Appropriate To study	Unbiased Endpoint Assessment	Follow-Up Adequate Period	<5% Lost- to Follow-Up	Study Size Population Calculation	Total MINORS Score	Confounding Factors LPRD	Tobacco	Allergy
Naunheim et al[12]	2	0	0	1	0	0	0	0	3	NP	NP	NP
Krishnan et al[13]	2	1	2	1	0	0	2	0	8	NP	13%	NP
Vance et al[14]	2	0	0	1	0	0	0	0	3	NP	NP	NP
Hong et al[15]	2	1	2	0	0	0	0	0	5	NP	NP	NP
Hassen and Hasseba[16]	2	0	2	2	1	0	0	0	7	70/280	39/280	55%
Pinto et al[17]	2	1	2	0	0	0	0	0	5	Treated with PPIs	NP	NP
Sahrawat et al[18]	2	0	2	1	1	1	0	0	7	20/38	12/38	NP
Kim et al[19]	2	0	2	2	1	1	0	0	8	NP	14%	NP
Erickson and Sivasankar[20]	2	0	2	1	1	1	2	0	9	Excluded	Excluded	Included
Bhalla et al[21]	2	1	2	0	0	0	0	0	5	Excluded	Excluded	Excluded
Stanton et al[22]	2	0	2	1	0	0	0	0	5	Excluded	Excluded	NP
Bhalla et al[23]	2	1	2	1	1	0	2	0	9	NP	Excluded	NP
Bhalla et al[24]	2	1	2	0	0	0	2	0	7	Excluded	Excluded	Included
Foster et al[25]	2	0	2	0	0	0	0	0	4	Excluded	Excluded	Included
Gallivan et al[26]	2	0	0	1	0	0	0	0	3	51% GERD	NP	NP
Mirza et al[27]	2	0	0	1	0	0	0	0	3	NP	NP	29/68
Ihre et al[28]	2	0	2	0	0	0	0	0	4	Excluded	NP	NP
Balter et al[29]	2	0	2	1	1	1	0	0	7	NP	NP	NP
Crompton et al[30]	2	0	2	2	1	1	0	0	8	NP	NP	NP
Williamson et al[31]	2	0	2	0	0	0	0	0	4	NP	44.5%	NP
Watkin and Ewanowski[32]	2	0	2	1	1	2	0	0	8	NP	NP	NP

Abbreviations: GERD, gastroesophageal reflux disease; LPRD, laryngopharyngeal reflux disease; NP, not provided.

commonly prescribed inhalers range from 1.1 to 4.5 μm.[33] The use of small particles (around 1 μm) can be associated with fewer adverse events because they predominantly reach distal airways.[34] The size of the particles is particularly important in the interpretation of the results of this review. The studies included reported substantial variability in the evaluated IC drugs. Pressurized meter hydrofluoroalkane suspension inhalers, including Fluticasone propionate, have larger particle sizes than pressurized metered-dose hydrofluoroalkane solution inhalers, such as Beclomethasone dipropionate, Flunisolide, and Ciclesonide, which can explain the variability of dysphonia incidence across studies in the present review.

The duration of IC therapy and the doses are additional factors that can explain potential discrepancies across studies. From a pathophysiological standpoint, ICs could be associated with dryness of the vocal folds and potential steroid-induced myopathy, which both lead to modifications of the biomechanical properties of the vocal folds and related voice quality impairments.[35] While this hypothesis is supported by VLS observations, including vocal fold dryness, supraglottic muscle tension, and vocal forcing in IC users,[13,14,16,19,26,27,36] there are no investigations of histological vocal fold changes in IC users or animal models. Interestingly, it has been suggested that the delivery system (metered-dose inhalers versus dry powder inhalers) could be a key factor in the development of dysphonia in IC users.[37] In a study of 154 patients who were treated for 2 years with an IC administered via metered-dose inhaler followed by 2 years of administration via dry powder inhalers, the frequency of hoarseness decreased from 21% to 6%.[37]

Some extrinsic factors can similarly influence the findings of studies. Laryngopharyngeal reflux disease, tobacco consumption, and allergy may constitute three prevalent confounding factors, which were poorly controlled in the studies. The VLS abnormalities identified in IC users are nonspecific and can be found in laryngopharyngeal reflux disease. Indeed, laryngopharyngeal reflux disease is commonly associated with mucosa dryness, endolaryngeal sticky mucus, and laryngopharyngeal erythema.[38–40] Similar to IC laryngitis, a pathophysiological model of reflux-induced dysphonia suggests that the macro- and microscopic vocal fold mucosa alterations related to reflux can be associated with modifications of the biomechanical properties of the vocal folds, leading to compensatory (forcing) vocal behaviors.[38] These similarities across both conditions highlight the importance of controlling for laryngopharyngeal reflux disease in studies investigating the impact of IC use on voice quality. Similar observations can be made for tobacco, which is associated with laryngopharyngeal mucosa inflammation and related functional impact.[41]

Although many authors did not report allergy findings, it is assumed that a significant number of patients with asthma and IC use have allergy, including allergic rhinitis. Allergic rhinitis and the related postnasal drip can be a confounding factor for throat symptoms and dysphonia in this population of patients. Future studies should compare the voice quality of allergic versus nonallergic IC users, while controlling for other intrinsic and extrinsic confounding factors. Furthermore, ICs can be prescribed in the treatment of chronic cough, which may incur its own changes to the vocal folds. The prevalence of patients with IC prescription related to chronic cough was not reported in studies, which is an additional confounding factor. In the same vein, most studies did not report nondysphonia adverse laryngeal events associated with IC use, such as candidiasis and fungal laryngitis. These factors need to be considered in future studies.

The increase of asthma triggers and the related increase of the incidence of asthma worldwide support the need to conduct future high-quality prospective longitudinal studies investigating multidimensional voice quality in IC users, while considering all confounding factors.

The primary outcome was voice quality in IC users. Voice quality was evaluated through a myriad of outcomes, mostly being unvalidated subjective assessments. Acoustic and aerodynamic outcomes were measured in some studies through several methods (type of vowel, vowel portion selection for acoustic measures, etc), which limits the drawing of valid conclusions. Voice quality was not assessed through recommended multidimensional validated approaches considering patient-reported and perceptual evaluations alongside acoustic and aerodynamic measurements.[11] Adherence to expert consensus on multidimensional voice quality assessment could substantially improve the understanding of pathophysiological mechanisms underlying the development of dysphonia in IC users.

The low quality of studies, the lack of multidimensional voice quality evaluations, and the heterogeneity across studies in terms of inclusion and exclusion criteria, drug features, outcomes, and follow-up are the primary limitations of this review. Despite substantial heterogeneity, the overall trends support an association between the use of ICs and the development of dysphonia in a moderate proportion of patients.

Future prospective longitudinal studies are needed to clarify the incidence of dysphonia in IC users and to understand the pathophysiological mechanisms underlying the development of dysphonia while considering numerous intrinsic and extrinsic confounding/influencing factors.

CONCLUSION

ICs significantly impact voice quality, with substantial discrepancy between patient-reported and clinician-reported dysphonia rates. The drug features influence the occurrence of dysphonia, despite methodological limitations. Future research requires standardized multidimensional voice quality assessments and better control of confounding factors to clarify the underlying pathophysiological mechanisms.

Institutional Review Board Statement

Not required.

Informed Consent Statement

Not applicable.

Author Contributions

Jerome R. Lechien: Design, acquisition of data, data analysis and interpretation, drafting, final approval, and accountability for the work; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

Not applicable.

Declaration of Competing Interest

The author has no financial interest in the subject under discussion. All authors have read and approved the paper. Would you be so kind to consider the present paper and send us the reviewer's comments?

Acknowledgments

None.

Supplementary Materials

None.

References

1. Shaw DE, Sousa AR, Fowler SJ, et al. U-BIOPRED Study Group. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J.* 2015;46:1308–1321. https://doi.org/10.1183/13993003.00779-2015.
2. Masoli M, Fabian D, Holt S, Beasley R. Global burden of asthma. 2004. Available at: http://www.ginasthma.com/ReportItem.asp?l1=2&l2=2. Accessed October 25, 2005.
3. Fuhlbrigge AL, Adams RJ, Guilbert TW, et al. The burden of asthma in the United States: level and distribution are dependent on interpretation of the national asthma education and prevention program guidelines. *Am J Respir Crit Care Med.* 2002;166:1044–1049. https://doi.org/10.1164/rccm.2107057.
4. Pinto CR, Almeida NR, Marques TS, Yamamura LL, Costa LA, Souza-Machado A. Local adverse effects associated with the use of inhaled corticosteroids in patients with moderate or severe asthma. *J Bras Pneumol.* 2013;39:409–417. https://doi.org/10.1590/S1806-37132013000400003.
5. Rachelefsky GS, Liao Y, Faruqi R. Impact of inhaled corticosteroid-induced oropharyngeal adverse events: results from a meta-analysis. *Ann Allergy Asthma Immunol.* 2007;98:225–238. https://doi.org/10.1016/S1081-1206(10)60711-9.
6. Galván CA, Guarderas JC. Practical considerations for dysphonia caused by inhaled corticosteroids. *Mayo Clin Proc.* 2012;87:901–904. https://doi.org/10.1016/j.mayocp.2012.06.022.
7. Thompson M, Tiwari A, Fu R, Moe E, Buckley DIA. *Frame-Work to Facilitate the Use of Systematic Reviews and Meta-Analyses in the Design of Primary Research Studies.* Rockville, MD: Agency for Healthcare Research and Quality,; 2012.
8. McInnes MDF, Moher D, Thombs BD, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. *JAMA.* 2018;319:388–396.12. Lyon guidelines.
9. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg.* 2011;128:305–310. https://doi.org/10.1097/PRS.0b013e318219c171.
10. Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg.* 2003;73:712–716. https://doi.org/10.1046/j.1445-2197.2003.02748.x.
11. Lechien JR, Geneid A, Bohlender JE, et al. Consensus for voice quality assessment in clinical practice: guidelines of the European Laryngological Society and Union of the European Phoniatricians. *Eur Arch Otorhinolaryngol.* 2023;280:5459–5473. https://doi.org/10.1007/s00405-023-08211-6.
12. Naunheim MR, Huston MN, Bhattacharyya N. Voice disorders associated with the use of inhaled corticosteroids. *Otolaryngol Head Neck Surg.* 2023;168:1034–1037. https://doi.org/10.1002/ohn.198.
13. Krishnan NV, Pujary K, Bhandarkar AM, Devadas U, Magazine R. Videostroboscopy and voice profile in long-term combination inhaler users with obstructive lower airway disease. *Otolaryngol Head Neck Surg.* 2022;166:927–932. https://doi.org/10.1177/01945998211031449.
14. Vance D, Alnouri G, Valentino W, Eichorn D, Acharya P, Sataloff RT. Effects of particle size of inhaled corticosteroid on the voice. *J Voice.* 2021;35:455–457. https://doi.org/10.1016/j.jvoice.2019.11.013.
15. Hong JY, Kim JH, Park S, Hwang YI, Jung KS, Jang SH. Efficacy and predictors of response to inhaled corticosteroid treatment for chronic cough. *Korean J Intern Med.* 2019;34:559–568. https://doi.org/10.3904/kjim.2017.291.
16. Hassen HE, Hasseba AMA. Voice evaluation in asthma patients using inhaled corticosteroids. *Kulak Burun Bogaz Ihtis Derg.* 2016;26:101–108. https://doi.org/10.5606/kbbihtisas.2016.79740.
17. Pinto CR, Almeida NR, Marques TS, Yamamura LL, Costa LA, Souza-Machado A. Local adverse effects associated with the use of inhaled corticosteroids in patients with moderate or severe asthma. *J Bras Pneumol.* 2013;39:409–417. https://doi.org/10.1590/S1806-37132013000400003.
18. Sahrawat R, Robb MP, Kirk R, Beckert L. Effects of inhaled corticosteroids on voice production in healthy adults. *Logoped Phoniatr Vocol.* 2014;39:108–116. https://doi.org/10.3109/14015439.2013.777110.
19. Kim HS, Moon JW, Chung SM, Lee JH. A short-term investigation of dysphonia in asthmatic patients using inhaled budesonide. *J Voice.* 2011;25:88–93. https://doi.org/10.1016/j.jvoice.2009.07.003.
20. Erickson E, Sivasankar M. Evidence for adverse phonatory change following an inhaled combination treatment. *J Speech Lang Hear Res.* 2010;53:75–83. https://doi.org/10.1044/1092-4388(2009/09-0024).
21. Bhalla RK, Taylor W, Jones AS, Roland NJ. The inflammation produced by corticosteroid inhalers in the pharynx in asthmatics. *Clin Otolaryngol.* 2008;33:581–586. https://doi.org/10.1111/j.1749-4486.2008.01837.x.
22. Stanton AE, Sellars C, Mackenzie K, McConnachie A, Bucknall CE. Perceived vocal morbidity in a problem asthma clinic. *J Laryngol Otol.* 2009;123:96–102. https://doi.org/10.1017/S002221510800323X.
23. Bhalla RK, Watson G, Taylor W, Jones AS, Roland NJ. Acoustic analysis in asthmatics and the influence of inhaled corticosteroid therapy. *J Voice.* 2009;23:505–511. https://doi.org/10.1016/j.jvoice.2007.11.001.
24. Bhalla RK, Jones AS, Roland NJ. Prevalence of pharyngeal and laryngeal complications in adult asthmatics using inhaled corticosteroids. *J Laryngol Otol.* 2008;122:1078–1083. https://doi.org/10.1017/S0022215107001272.

25. Foster JM, van Sonderen E, Lee AJ, et al. A self-rating scale for patient-perceived side effects of inhaled corticosteroids. *Respir Res.* 2006;7:131. https://doi.org/10.1186/1465-9921-7-131.
26. Gallivan GJ, Gallivan KH, Gallivan HK. Inhaled corticosteroids: hazardous effects on voice-an update. *J Voice.* 2007;21:101–111. https://doi.org/10.1016/j.jvoice.2005.09.003.
27. Mirza N, Kasper Schwartz S, Antin-Ozerkis D. Laryngeal findings in users of combination corticosteroid and bronchodilator therapy. *Laryngoscope.* 2004;114:1566–1569. https://doi.org/10.1097/00005537-200409000-00012.
28. Ihre E, Zetterström O, Ihre E, Hammarberg B. Voice problems as side effects of inhaled corticosteroids in asthma patients–a prevalence study. *J Voice.* 2004;18:403–414. https://doi.org/10.1016/j.jvoice.2003.05.003.
29. Balter MS, Adams SG, Chapman KR. Inhaled beclomethasone dipropionate improves acoustic measures of voice in patients with asthma. *Chest.* 2001;120:1829–1834. https://doi.org/10.1378/chest.120.6.1829.
30. Crompton GK, Sanderson R, Dewar MH, et al. Comparison of Pulmicort pMDI plus Nebuhaler and Pulmicort Turbuhaler in asthmatic patients with dysphonia. *Respir Med.* 2000;94:448–453. https://doi.org/10.1053/rmed.1999.0762.
31. Williamson IJ, Matusiewicz SP, Brown PH, Greening AP, Crompton GK. Frequency of voice problems and cough in patients using pressurized aerosol inhaled steroid preparations. *Eur Respir J.* 1995;8:590–592.
32. Watkin KL, Ewanowski SJ. Effects of aerosol corticosteroids on the voice: triamcinolone acetonide and beclomethasone dipropionate. *J Speech Hear Res.* 1985;28:301–304. https://doi.org/10.1044/jshr.2802.301.
33. Perkins EL, Basu S, Garcia GJM, Buckmire RA, Shah RN, Kimbell JS. Ideal particle sizes for inhaled steroids targeting vocal granulomas: preliminary study using computational fluid dynamics. *Otolaryngol Head Neck Surg.* 2018;158:511–519. https://doi.org/10.1177/0194599817742126.
34. El Baou C, Di Santostefano RL, Alfonso-Cristancho R, et al. Effect of inhaled corticosteroid particle size on asthma efficacy and safety outcomes: a systematic literature review and meta-analysis. *BMC Pulm Med.* 2017;17:31. https://doi.org/10.1186/s12890-016-0348-4.
35. Buhl R. Local oropharyngeal side effects of inhaled corticosteroids in patients with asthma. *Allergy.* 2006;61:518–526. https://doi.org/10.1111/j.1398-9995.2006.01090.x.
36. Williams AJ, Baghat MS, Stableforth DE, Cayton RM, Shenoi PM, Skinner C. Dysphonia caused by inhaled steroids: recognition of a characteristiclaryngeal abnormality. *Thorax.* 1983;38:813–821. https://doi.org/10.1136/thx.38.11.813.
37. Selroos O, Backman R, Forsen KO, et al. Local side-effects during 4-year treatment with inhaled corticosteroids—a comparison between pressurized metered-dose inhalers and Turbuhaler. *Allergy.* 1994;49:888–890.
38. Lechien JR, Saussez S, Harmegnies B, Finck C, Burns JA. Laryngopharyngeal reflux and voice disorders: a multifactorial model of etiology and pathophysiology. *J Voice.* 2017;31:733–752. https://doi.org/10.1016/j.jvoice.2017.03.015.
39. Carroll TL. Reflux and the voice: getting smarter about laryngopharyngeal reflux. *Otolaryngol Clin North Am.* 2019;52:723–733. https://doi.org/10.1016/j.otc.2019.03.015.
40. Lechien JR, Finck C, Costa de Araujo P, et al. Voice outcomes of laryngopharyngeal reflux treatment: a systematic review of 1483 patients. *Eur Arch Otorhinolaryngol.* 2017;274:1–23. https://doi.org/10.1007/s00405-016-3984-7.
41. Jetté ME, Seroogy CM, Thibeault SL. Laryngeal T regulatory cells in the setting of smoking and reflux. *Laryngoscope.* 2017;127:882–887. https://doi.org/10.1002/lary.26223.