ORIGINAL RESEARCH

Self-reported throat symptoms in Ehlers–Danlos syndromes and hypermobility spectrum disorders: A cross-sectional survey study

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Abstract

Objectives: This study identified the frequency and severity of dysphagia, dysphonia, and laryngopharyngeal reflux symptoms in people with Ehlers–Danlos syndromes (EDS) or hypermobility spectrum disorders (HSD) and explored differences between diagnostic groups.

Methods: Participants were recruited via non-probability convenience sampling. Information was gathered via online survey, including the Reflux Symptom Index (RSI; Belafsky et al., *J Voice*. 2002;16:274–277), the Eating and Drinking Assessment Tool (EAT-10; Belafsky et al., *Ann Otol Rhinol Laryngol*. 2008;117:919–924), and the Voice Handicap Index (VHI; Jacobson et al., *Am J Speech Lang Pathol*. 1997;6(3):66–70). These were analyzed using ANOVAs.

Results: There were 1620 participants (96.6% female, 2.8% male) that met the inclusion criteria. The mean age was 38.09 (SD 12.22). 75.51% had hypermobile EDS (hEDS), 17.83% had HSD and 3.33% had classic EDS (cED). The cohort's mean scores were RSI = 22.95 (SD 9.01), EAT-10 = 11.91 (SD 9.66), and VHI score = 31.99 (SD 24.36). The hEDS group had significantly higher mean scores than the HSD group on RSI score and on some RSI items, on EAT-10 score and on all EAT-10 items, and on one VHI item.

Conclusion: People with EDS/HSD experience symptoms of acid reflux, dysphagia, and dysphonia to varying degrees with significant differences between hEDS than HSD. Awareness of the impact of EDS/HSD on throat symptoms will enable health care professionals to anticipate throat symptoms more readily in this population, providing individualized and effective management plans.

Level of Evidence: IV.

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1 | INTRODUCTION

Ear, nose, and throat (ENT) specialists at a laryngology clinic in the United Kingdom have found an increase in referrals for patients with Ehlers–Danlos syndromes (EDS) experiencing symptoms of dysphagia, dysphonia and laryngopharyngeal reflux (LPR).

The Ehlers–Danlos syndromes are heritable disorders of connective tissue (HDCT), characterized by joint hypermobility, skin hyperextensibility and tissue fragility and there are 13 distinct subtypes.[1] Hypermobile EDS (hEDS) is the most common subtype, likely representing >90% of cases, with a prevalence presumed at around 1/3500.[2] EDS presents with many comorbidities including pain, fatigue, anxiety, gastro-intestinal issues, autonomic dysfunction, temporomandibular joint disorder (TMJD), and dental issues.[3] Hypermobility spectrum disorders (HSD) are joint hypermobility related conditions that do not meet the diagnostic criteria for hEDS or any other HDCT. Recent studies of EDS and HSD demonstrated that, between them, the prevalence of the above comorbidities is similar.[4,5] The diagnosis of EDS pre 2017 would have been by the Villefranche criteria,[6] and post 2017 by the International Criteria,[1] which involve looking for various signs of connective tissue pathology including tissue laxity and fragility. In addition, many comorbidities are seen that are not in the diagnostic criteria and include inflammation for example, mast cell activation, GERD, and neuropathy among others.

To our knowledge, there are two published quantitative studies of dysphagia and dysphonia in EDS to date. A survey-based study of people with EDS identified dysphagia in 39% of respondents and dysphonia symptoms in 27% of respondents.[7] Most published research into this area has been case study based.[8–10] Gastro-intestinal symptoms in EDS have been well documented with a study finding gastroesophageal reflux disease (GORD) reported in 68.7% of their patients.[11] Given the relationship between GORD and LPR, it is reasonable to consider whether LPR may also be a symptom of EDS, which may affect swallowing and voicing.

Further research into throat symptoms of EDS and HSD could inform assessment and treatment for this population. This study aimed to identify the frequency and severity of throat symptoms (i.e., dysphonia, dysphagia, and LPR/upper airway inflammation) in this population.

2 | MATERIALS AND METHODS

This was a cross-sectional observational study. Information was gathered via an online survey using Qualtrics (Provo, UT). Participants who reported a diagnosis of EDS or HSD, aged 18 or over, and able to complete the survey in English were included. Participants were recruited via non-probability snowball sampling (a convenience

sample). They were primarily recruited via EDS and hypermobility organizations: the Ehlers–Danlos Society, Ehlers–Danlos Support UK, and the Hypermobility Syndromes Association. These organizations advertised the study on social media, on their websites, and via e-newsletter. The researcher also advertised the study on Twitter. Ethical approval was obtained from City, University of London (ref. ETH2021-0526). The survey could be completed from 11th February–9th May 2021 inclusive, after completing an informed consent form, either online or by completing a pdf/printed copy of the survey and returning it via email or post.

2.1 | Measures

Clinical data were gathered including age, country of residence, gender, education level, employment status, and type of EDS. The survey included patient reported outcome measures (PROMs) that are routinely used to identify the presence and severity of LPR, dysphagia and dysphonia: the Reflux Symptom Index,[12] the Eating Assessment Tool,[13] and the Voice Handicap Index.[14] The RSI measure was used with caution as it should be noted that it measures severity of symptoms associated with upper airway inflammation including but not exclusive to those of LPR. With this in mind, a high RSI score in isolation does not determine the presence of LPR. The VHI consists of three subscales, measuring the Emotional (VHI-E), Functional (VHI-F), and Physical (VHI-P) impact of dysphonia. Participants were also asked if they had been diagnosed with any of four ENT conditions that had clinically been associated with EDS: TMJ, tracheomalacia/tracheostenosis, Eagle syndrome, and atlanto-axial spine subluxation (AAS).

According to authors of the measures, an RSI score of 13 or above may indicate significant LPR[12] and an EAT-10 score of 3 or above may indicate difficulties swallowing efficiently and safely,[13] so these figures were used as threshold scores respectively.

2.2 | Statistical/analytical strategy

The frequency and impact of dysphonia (based on VHI score), frequency and severity of LPR (based on RSI score) and frequency and severity of dysphagia (based on EAT-10 score) symptoms in participants were recorded using descriptive statistics. For categorical data (EDS/HSD diagnosis, gender, residing country, education level, employment, and diagnosis of ENT conditions) frequency and percentages were utilized. For continuous scales (age, RSI, VHI, EAT-10), mean scores and standard deviations (SD) were reported. Frequency and percentages and one-sample t-tests were also utilized to report cases that met PROM thresholds outlined in Table 1.

TABLE 1 Patient reported outcome measures used to measure laryngopharyngeal reflux (LPR), dysphagia, dysphonia, and ear, nose, and throat symptoms.

Outcome measure	Condition measured	Number of items	Response scale	Scoring range	Score thresholds
Reflux Symptom Index[12]	LPR	9	0 (no problem) to 5 (severe problem)	0–45	≥13 may indicate severe reflux
Eating Assessment Tool[13]	Dysphagia	10	0 (no problem) to 4 (severe problem)	0–40	≥3 may indicate problems swallowing efficiently and safely
Voice Handicap Index[14]	Impact of dysphonia	30	0 (never) to 4 (always)	0–120	0–30 = mild 31–60 = moderate 61–120 = severe

TABLE 2 Descriptives for patient reported outcome measures (PROMs) based on whole Ehlers–Danlos syndrome/hypermobility spectrum disorder cohort.

PROM	N	Minimum	Maximum	Mean	SE of mean	SD	Skewness	SE of skewness
RSI	1620	1	45	22.95	0.22	9.01	−0.05	0.06
EAT-10	1581	0	40	11.91	0.24	9.66	0.75	0.06
VHI	1532	0	116	31.99	0.62	24.36	0.75	0.06
VHI-E	1532	0	40	8.26	0.23	8.95	1.11	0.06
VHI-F	1549	0	40	9.60	0.23	9.09	0.93	0.06
VHI-P	1543	0	40	14.77	0.23	8.97	0.21	0.06

Abbreviations: EAT-10, Eating and Drinking Assessment Tool[13]; RSI, Reflux Symptom Index[12]; SE, standard error; VHI, Voice Handicap Index[14]; VHIE, VHI Emotional subset; VHIF, VHI Functional subset; VHIP, VHI Physical subset.

Comorbidity differences (ENT diagnoses) were explored using chi-squared (χ^2) tests using Cramer's phi (ϕ) as a measure of association. Group differences between RSI scores, EAT-10 scores, VHI scores were explored using ANOVAs, based on both total scores and at item (individual question) level. Post hoc tests (Tukey) were performed to identify significant differences between groups. Partial eta squared (η_p^2) was used to measure overall effect size (ES) and Hedge's g was calculated to measure ES between two groups at a time. Statistical significance was measured at the $p < .01$ level. Statistical analyses were conducted in SPSS v28 (IBM Corp., Armonk, NY). A sample size calculation in G*Power 3[15] indicated that to find a medium effect size ($f = 0.25$) difference between three groups (hEDS, HSD, and cEDS), at alpha .01 and power 90%, within an ANOVA, a sample size of 285 would be required (95 per group).

3 | RESULTS

3.1 | Demographics

There were 1620 participants who met the inclusion criteria. 1405 (86.73%) participants completed the survey in full and 215 (13.27%) completed it partially, all of which were included in the final sample. Missing data were dealt with by omitting partially completed PROMs (<50% of items per scale) from total score calculations and statistical tests/analyses. For partially completed PROMs of >50%, mean scores were calculated based on their partial score.

There were 1565 females (96.6%) and 46 males (2.8%), meaning gender comparisons were not appropriate. Participants were aged between 18 and 80 years with a mean age of 38.09 (SD 12.22). Most participants had a diagnosis of hEDS ($N = 1224$, 75.51%), followed by HSD ($N = 289$, 17.83%), and then cEDS ($N = 54$, 3.33%) (breakdown in composition of participant diagnoses are in Supplementary Information Table I). Analyses of variance were only explored between these three groups due to the small sample sizes of the other groups. Participants were recruited internationally. Most resided in the UK/CD (53.6%) or USA/Canada (31.9%).

3.2 | Throat symptoms in EDS/HSD cohort

With an RSI score of 13 or higher, 86.1% ($N = 1390$) of the cohort indicated that they may have severe LPR. A one sample t-test showed that the cohort's mean RSI score of 22.95 (SD 9.01) is significantly higher than the RSI threshold score of 13, $t(1619) = 44.41$, $p < .001$, suggesting the cohort experience LPR to a severe degree (Table 2).

With an EAT-10 score of 3 or above, 79.4% ($N = 1285$) indicated that they may have problems swallowing. A one sample t-test showed that the cohort's mean EAT-10 score of 11.91 (SD 9.66) is significantly higher than the EAT-10 threshold score of 3, $t(1580) = 36.69$, $p < .001$, suggesting that the cohort experience dysphagia to a severe degree with a wide distribution of scores (Table 2).

In terms of dysphonia, 53.4% of the EDS/HSD cohort had a VHI score of 0–30 (indicating a mild impact caused by dysphonia), 32.6%

had a VHI score of 31–60 (indicating a moderate impact), and 14.6% had a VHI score of 61–120 (indicating a severe impact caused by dysphonia). The VHI-E mean score was the lowest of the three subscales, followed by the VHI-F and the VHI-P mean score (Table 2). A one sample t-test showed that the cohort's mean VHI score of 31.99 (SD = 24.36) is significantly lower than the VHI threshold score of 61 to indicate a severe impact, $t(1531) = -46.6$, $p < .001$. Their mean VHI score suggested that, overall, the cohort experience a mild to moderate impact of the dysphonia with a wide distribution of scores (Table 2).

3.3 | Differences between diagnostic groups

3.3.1 | Co-morbidity differences

The most common ENT comorbidity was TMJD. There was a significant difference in number of people diagnosed with TMJD (χ^2 (2) = 25.839; $p < .001$), occurring most frequently in the hEDS group (57.3%), followed by the cEDS group (45.1%) and the HSD group (40.3%) with a moderate strength of association ($\phi = 0.135$). There was a significant difference in number of people diagnosed with AAS, (χ^2 (2) = 12.403; $p = .002$) occurring most frequently in the HSD group (19.6%), followed by the hEDS group (10%) and the cEDS group (5%) with a weak strength of association ($\phi = .093$). Statistical tests

were not appropriate for comparing diagnosis of Eagle syndrome or tracheomalacia/tracheal stenosis due to the small numbers but 1/51 of the cEDS group, 14/1113 of the hEDS group and 3/258 of the HSD group had been diagnosed with Eagle syndrome. 4/51 of the cEDS group, 41/1113 of the hEDS group and 5/258 of the HSD group had been diagnosed with tracheomalacia/tracheal stenosis. Frequency and analysis results are in Table 3.

3.3.2 | Reflux symptom differences (RSI)

All three group (cEDS, hEDS, and HSD) mean RSI scores were markedly higher than the threshold of 13, with wide distributions of scores (Table 4). There was a significant difference in RSI mean score with the hEDS group scoring highest, followed by the cEDS group, and the HSD group with a small ES ($\eta_p^2 = 0.012$). Post hoc comparisons revealed the hEDS group scored significantly higher than the HSD group with a small ES ($g = 0.29$). Statistics are in Table 4. On item level analysis, there were significant differences in RSI-2 "clearing your throat" ($p = .002$), RSI-4 "difficulty swallowing food, liquids or pills" ($p < .001$), and RSI-6 "breathing difficulties or choking episodes" ($p = .001$), scores with post hoc tests revealing significantly higher scores in hEDS than HSD with a small ES ($g = 0.18$–0.29). There were also significant differences in RSI-9 score although no significance was revealed in post hoc comparisons. There were no significant

TABLE 3 Group differences in additional ear, nose, and throat-related diagnosis.

Variable		cEDS Freq. n	%	hEDS Freq. n	%	HSD Freq. n	%	Chi squared statistics Pearson's $\chi^2_{(df2)}$	p	Cramer's ϕ
Temporomandibular joint disorder (TMJD)	Yes	23	45.1	638	57.3	104	40.3	25.839	<.001	0.135
	No	28	54.9	476	42.7	154	59.7			
Eagle syndrome	Yes	1	2	14	1.3	3	1.2	0.220	.896	0.012
	No	50	98	1099	98.7	255	98.8			
Tracheomalacia/tracheal stenosis	Yes	4	7.8	41	3.7	5	1.9	4.801	.091	0.058
	No	47	92.2	1072	96.3	253	98.1			
Atlanto-axial subluxation (AAS)	Yes	10	19.6	111	10	13	5	12.403	.002	0.093
	No	41	80.4	1002	90	245	95			

TABLE 4 Patient reported outcome measure (PROM) mean scores and ANOVA statistics for cEDS, hEDS, and HSD.

PROM	cEDS Mean	SD	hEDS Mean	SD	HSD Mean	SD	ANOVA statistics $F_{(2,df2)}$	Df2	p	η_p^2	ES (Hedge's g) hEDS versus HSD	hEDS versus cEDS	HSD versus cEDS
RSI	22.67 [a,b]	10.11	23.44 [a]	8.85	20.85 [b]	9.16	9.810	1564	<.001	0.012	0.29	0.09	−0.19
EAT-10	11.51	10.76	12.56 [a]	9.78	9.05 [b]	8.29	14.91	141.47 [A]	<.001	0.020	0.37	0.11	−0.28
VHI	31.90	27.40	32.73	24.56	28.81	22.97	2.829	1480	.059	0.004	0.16	0.03	−0.13

Abbreviations: EAT-10, Eating and Drinking Assessment Tool[13]; ES, Effect Size; RSI, Reflux Symptom Index[12]; SD, standard deviation; VHI, Voice Handicap Index.[14]
[A]Brown–Forsythe ANOVA reported. Superscript letters indicate post hoc test results (Tukey) show significant differences between groups. Italicized values indicate significant p value ($p = .01$).

differences in other RSI items. Statistics for item level analyses are in Supplementary Information Table II.

3.3.3 | Dysphagia symptom differences (EAT-10)

All three group (cEDS, hEDS, and HSD) mean EAT-10 scores were markedly higher than the threshold of 3, with wide distributions of scores (Table 4). There was a significant difference in EAT-10 mean score with the hEDS group scoring highest followed by the cEDS group and the HSD group with a small ES ($\eta_p^2 = 0.02$) (statistics reported in Table 4). Post hoc comparisons revealed a significantly higher mean EAT-10 score in hEDS than HSD with a small to medium ES ($g = 0.37$). At item level, there were significant differences in all 10 items ($p \leq .001–.001$) with small ES ($\eta_p^2 = 0.01–0.018$) with hEDS scoring significantly higher than HSD ($g = 0.24–34$). Statistics for item level analyses are in Supplementary Information Table III.

3.3.4 | Dysphonia related QoL (VHI)

The cEDS group mean VHI score and the hEDS mean score indicated a moderate impact caused by dysphonia, whereas the HSD mean VHI score indicated a mild impact caused by dysphonia, and all three groups had a wide distribution of scores (Table 4). There were no significant differences in scores on the VHI (Table 4), VHIE, VHIP or VHIF scales. At item level, there was a significant difference in scores on item VHI-P4 ("My voice is creaky and dry") ($p = .003$) with the hEDS group scoring highest followed by HSD group and the cEDS group with a negligible ES ($\eta_p^2 = 0.008$), but there were no significant differences in mean scores between groups on post hoc comparisons. There were no significant differences in scores for the other VHI items. Statistics for item level analyses and VHI subscales are in Supplementary Information Table IV.

4 | DISCUSSION

This study revealed that people with EDS and HSD experience symptoms of LPR/upper-airway inflammation, dysphagia, and dysphonia to varying degrees. There were subtle but distinct significant differences in severity of throat symptoms between hEDS and HSD.

The EDS/HSD cohort's mean RSI score of 22.95 (SD 9.0) indicates that LPR-like symptoms are common in people with EDS/HSD. Their mean score is substantially higher than that of 91 asymptomatic subjects in a study by Chen et al., which was 2.24 (SD 2.34).[16] In drawing comparisons between diagnostic groups, the hEDS group's significantly higher mean RSI total score than the HSD group suggests that, whereas both groups experience LPR-like symptoms to a degree, they are experienced more severely in people with hEDS. Item level analyses indicated the hEDS group displayed significantly higher scores on RSI items, "clearing your throat," "difficulty swallowing food, liquids or pills," and "breathing difficulties or choking episodes."

The EAT-10 score findings suggest that people with EDS/HSD experience more severe swallowing difficulties than the non-dysphagic population. Compared to normative data,[13] the EDS/HSD cohort's mean EAT-10 score of 11.91 (SD 9.65) was substantially higher than "healthy" individuals and closest to those experiencing reflux and dysphonia. In drawing comparisons between hEDS, cEDS and HSD, significant differences were only found between the hEDS group and the HSD group, with the hEDS group displaying significantly higher mean scores on their overall EAT-10 total scores and on all 10 EAT-10 items. This suggests that, whereas both groups experience swallowing difficulties to a degree, they are experienced more severely in people with hEDS.

The VHI scores showed that people with EDS/HSD experience dysphonia to varying degrees. The cohort's mean VHI score at 31.99 (SD 24.36) is lower than that found in a study of 109 people with functional dysphonia, which was 71.[17] It is also lower than the mean score found by Bouwers and Dikkers[18] in people with benign voice disorders prior to treatment at 48.9 (SD 20.9) but substantially higher than their control group at 3.6 (SD 3.8). Although there is a strong association between anxiety disorders and hEDS/HSD,[19] the mean VHI subscale scores (VHI-E, VHI-F, and VHI-P) indicated that people with EDS/HSD are impacted by voice difficulties on a more physical level than on a functional or emotional one. There were no significant differences in mean VHI score between groups. However, the significant difference between hEDS and HSD on the item, "My voice is creaky and dry," suggests that oropharyngeal dryness is experienced more frequently in people with hEDS than HSD.

The voice difficulties experienced by participants could be explained by the recently reported multifactorial causes of dysphonia in EDS/HSD that indicate, (i) the incoordination or hypermobility of the vocal cords, (ii) reduced mobility of the cricoarytenoid joint, and (iii) loss of mucosal wave due to changes in the collagen contributing to the fine surface vibration of the vocal folds (cords), are possible mechanisms by which one's voice may be affected.[20]

As the largest study of its kind in terms of exploring throat symptoms of EDS/HSD and self-management strategies, this work provides a unique and valuable contribution and has generated interest from leading health care practitioners specializing in EDS and HSD. Prior to this study, throat symptoms of EDS/HSD have not been well reported or characterized.[20]

Recruitment of participants was highly successful for the cEDS, hEDS, and HSD groups, resulting in a large sample and strong reliability of results for these groups as well as allowing comparisons to be drawn between them. The small sample size obtained for the rarer types of EDS is likely to reflect the rarity of these conditions, the prevalence of which is not known.[21] The vast disparity in numbers of female to male participants meant that gender comparisons were not appropriate. However, the ratio of female to male is typical of EDS specialty clinics (author's experience [AJH]).

The throat outcome measures used in this study (RSI, EAT-10, and VHI) are those recommended by Birchall et al.,[20] who argue that surgeons seeing EDS patients should use these same measures so that comparisons can be made in terms of severity of condition and disease outcomes. However, the RSI in particular does not replace a

thorough history, examination and testing[22] and should not be used in isolation to diagnose LPR. It is likely that the RSI scores represent a general marker of throat health, rather than being completely specific for extra-esophageal reflux. To a lesser extent, similar caveats can be applied to the VHI and the EAT-10 systems too.

5 | CONCLUSION

People with EDS/HSD experience symptoms of acid reflux, dysphagia and dysphonia to varying degrees with symptoms experienced more severely in hEDS than HSD. Awareness of the impact of EDS/HSD on throat symptoms will enable health care practitioners to anticipate throat symptoms more readily in this population and provide individualized and more effective management plans for their patients. These findings may also act as a guide toward better diagnostic criteria of hEDS and HSD throat symptoms in future.

CONFLICT OF INTEREST STATEMENT

Alan J. Hakim has received honoraria for education work and conference presentations undertaken for The Ehlers–Danlos Society.

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SUPPORTING INFORMATION

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