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Similarities and differences in self-reported symptoms and comorbidities between hypermobile Ehlers–Danlos syndrome and hypermobility spectrum disorders

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Abstract

Objectives: Patients with hypermobile Ehlers–Danlos syndrome (hEDS) and hypermobility spectrum disorders (HSD) experience a wide array of symptoms and system disorders. This study aimed to identify whether differences occurred in 115 self-reported symptoms and comorbidities in patients diagnosed with hEDS or HSD.

Methods: In this study we analysed self-reported data from an EDS Clinic intake questionnaire in patients diagnosed with hEDS, HSD or no hypermobile conditions.

Results: From 1 November 2019 to 7 March 2024, the EDS Clinic saw 2088 patients. Using the 2017 diagnostic criteria, 66.5% were diagnosed with HSD ($n=1389$), 20.3% with hEDS ($n=423$), 10.6% with historic HSD (H-HSD) or localized HSD (L-HSD) ($n=256$) (hypermobile controls) and 2.6% were not diagnosed with hEDS, HSD, H-HSD or L-HSD ($n=55$) (controls). Symptoms/comorbidities that occurred with high prevalence in both hEDS and HSD included joint pain (hEDS 82.0%, HSD 88.9%), allergy (hEDS 77.0%, HSD 77.0%), subluxations (hEDS 71.2%, HSD 72.6%), brain fog (hEDS 70.0%, HSD 74.7%), headache (hEDS 68.1%, HSD 69.1%), anxiety (hEDS 60.3%, HSD 69.3%), depression (hEDS 52.2%, HSD 58.0%), migraine (hEDS 53.7%, HSD 52.5%), nausea (hEDS 54.6%, HSD 59.5%) and constipation (hEDS 53.0%, HSD 57.2%). In contrast, 9/115 (8%) symptoms/comorbidities were self-reported significantly more often in hEDS but 42/115 (37%) in HSD. hEDS patients reported more symptoms that suggest a defect in collagen, such as dislocation, hernias and rectal prolapse, while HSD patients reported more joint, muscle, allergy, neurological, gastrointestinal, sleep and psychological symptoms/comorbidities.

Conclusion: Although we found an overlap in some symptoms and comorbidities self-reported by hEDS/HSD patients, such as allergy/atopy, headache/migraine and gastrointestinal symptoms, our findings suggest key differences exist between the two diagnoses, suggesting that hEDS and HSD may be distinct conditions.

Lay Summary

What does this mean for patients?

In 2017, new diagnostic criteria for hypermobile Ehlers–Danlos syndrome (hEDS) were published that created a separate diagnosis termed hypermobility spectrum disorders (HSD) based on a distinguishing set of clinical criteria. Since that time, clinicians and researchers have debated whether the myriad of symptoms and comorbidities that are associated with this condition differ in patients diagnosed with hEDS or HSD

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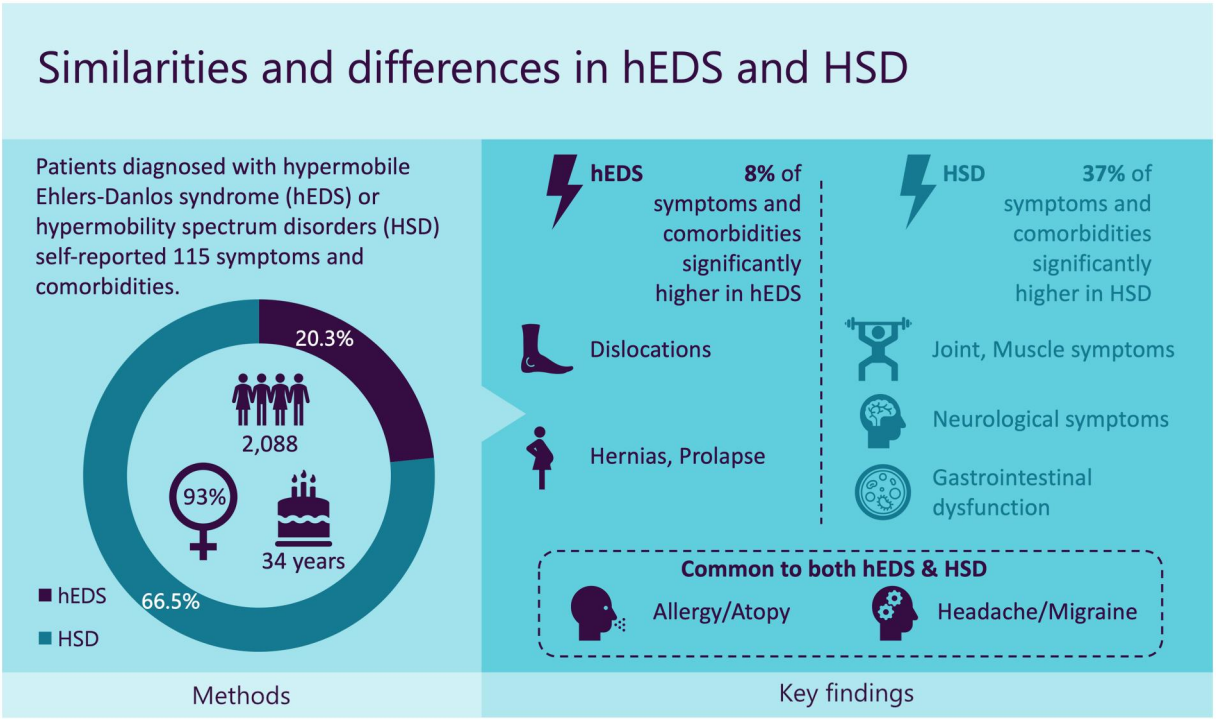
using the 2017 criteria. The goal of this study was to compare >100 self-reported symptoms and comorbidities from different organs or systems from >2000 patients diagnosed using the 2017 criteria compared with controls. We found that several symptoms and comorbidities occurred with both diagnoses, such as allergy, partial dislocation of joints and headache/migraine. However, we also found distinct differences between symptoms/comorbidities between the two diagnoses. hEDS patients reported more symptoms that suggest a defect in collagen, such as dislocation, hernias and rectal prolapse, while HSD patients reported more joint, muscle, neurological, gastrointestinal, sleep and psychological symptoms/comorbidities. These findings suggest that hEDS and HSD may be distinct conditions.

Graphical abstract



RHEUMATOLOGY ADVANCES IN PRACTICE

Darakjian *et al.* Similarities and differences in self-reported symptoms and comorbidities between hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders.

Keywords: hypermobile Ehlers–Danlos syndrome, hypermobility spectrum disorders, comorbidities, pain, allergy, headache, migraine.

Key messages

- The top five comorbidities that occurred in both hEDS and HSD were allergy, subluxation, headache, sprains and migraine.
- Patients with HSD reported more joint, muscle, allergy, neurological, gastrointestinal, sleep and psychological symptoms than those with hEDS.
- Patients with hEDS reported more dislocations, autonomic dysfunction, hernias and prolapse than those with HSD.

Introduction

Hypermobile Ehlers–Danlos syndrome (hEDS) and hypermobility spectrum disorders (HSD) are heritable collagen disorders with widespread distribution of fragile connective tissue in the skin, joints, ligaments and internal organs [1]. A total of 255 million people worldwide (3%) are estimated to have hEDS/HSD [2]. Gene variants unique to hEDS/HSD are unknown except for a recent preprint report of mutations in the kallikrein gene family in patients with hEDS [3]. Diagnosis is based on strict physical criteria developed by the International EDS Consortium [4]. Patients diagnosed with hEDS/HSD have been reported to have significantly greater joint pain, musculoskeletal pain and fatigue than the general population [5, 6]. We previously reported that 56% of hypermobile patients seen at our EDS Clinic were also diagnosed with fibromyalgia, a disorder associated with joint pain and fatigue [7]. Comorbidities/symptoms of hypermobile patients are often multiorgan, multifaceted and potentially debilitating [1, 2].

A question that has arisen since the implementation of the new diagnostic criteria in 2017 is whether the criteria would identify two different patient groups or whether the two conditions were essentially an indistinguishable spectrum of

disease, suggesting that the criteria were somewhat arbitrary. Inherent in that perspective was the interpretation that patients with hEDS were more severe than patients with HSD. Few studies have analysed a large number of symptoms and comorbidities associated with hEDS and HSD separately due to the common diagnostic criteria of generalized joint hypermobility based on an age specific Beighton score and the view that hEDS and HSD are a phenotypic spectrum [4]. HSD may incorrectly be assumed to be less severe than hEDS based on this perspective and previous studies [8, 9]. One study analysed hEDS and HSD separately using the 2017 diagnostic nosology but did not find significant differences between the two conditions for most comorbidities [10]. In contrast, another study using the 2017 diagnostic criteria found significant differences in chronic fatigue, gastrointestinal (GI), neurologic and allergy/atopy symptoms/comorbidities examining ≈100 patients/diagnosis [11]. The Ehlers–Danlos Society has a registry of >10 000 patients with hEDS and HSD and is actively conducting research to determine whether symptoms and multisystem comorbidities are similar or different to determine whether the 2017 diagnostic criteria for hEDS and HSD should be revised [12, 13]. Our study aimed to examine >100 self-reported symptoms and comorbidities in a database of >2000 hEDS and HSD patients seen at a dedicated academic hypermobility clinic diagnosed using the 2017 diagnostic criteria to better understand whether similarities or differences exist between the diagnoses.

Methods

Patients

Patients were seen at the Mayo Clinic Florida EDS Clinic from 1 November 2019 to 7 March 2024 ($n=2088$). Patients attended the EDS Clinic by self-referral or referrals from inside or outside the Mayo Clinic. Patients seen at the EDS Clinic received a diagnosis of hEDS, HSD or neither diagnosis (control) according to the 2017 diagnostic criteria [4], as previously [7]. Controls were separated into those diagnosed with historical HSD (H-HSD), localized HSD (L-HSD) ($n=221$) or none of these diagnoses ($n=55$). H-HSD patients self-report that they previously met criteria for hEDS or HSD but, typically due to age, no longer meet the criteria. Hypermobility is known to decrease with age. L-HSD patients have hypermobility in joints other than those that are assessed for the 2017 diagnostic criteria and so they are 'hypermobile' but do not meet the criteria for a diagnosis of hEDS or HSD. Thus the patient groups in this study included controls ($n=55$), hypermobile controls (H-HSD and L-HSD; $n=221$), hEDS ($n=423$) and HSD ($n=1389$).

Controls

Previously we reported that patients seen at the EDS Clinic who were not diagnosed with hEDS or HSD using the 2017 diagnostic criteria were significantly different for most symptoms and comorbidities compared with diagnosed patients [7], suggesting that this group may serve as appropriate controls. However, this control group contains patients identified with H-HSD or L-HSD. To better understand whether control groups differed, we compared the two control groups for key symptoms and comorbidities. We found significant differences for many symptoms and comorbidities between 'hypermobile' controls (i.e. H-HSD and L-HSD) and controls with no hypermobile diagnoses (Table 1). For this reason, the control group that we used for this analysis was patients that attended the EDS Clinic but were not diagnosed with hEDS, HSD, H-HSD or L-HSD ($n=55$).

EDS Clinic data collection

Patient data were collected from 1 November 2019 to 7 March 2024 ($n=2088$). Patients received a 200-question REDCap intake questionnaire as the standard of care prior to their first appointment at the Mayo Clinic Florida EDS Clinic. Self-reported data were obtained from the intake questionnaire of adult patients >18 years of age. The intake questionnaire categorized questions by organ or system, such as muscles, joints, allergy, neurological symptoms or GI symptoms. Data are organized herein according to those organ or system categories.

Statistical analysis

Continuous variables were summarized with the sample median and range. Categorical variables were summarized with number and percentage of subjects. The Kruskal–Wallis rank sum test was used to compare the difference in continuous variables among groups. A chi-squared test examined the association between two categorical variables. All the tests were two-tailed and P-values <0.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Ethics statement

The Institutional Review Board (IRB 19-010260) of the Mayo Clinic approved the retrospective analysis of demographic and clinical data from medical records for this study and waived informed consent for all patients. The research conformed to the principles outlined in the Declaration of Helsinki.

Results

Patient demographics

From the 2088 patients who were assessed for hEDS or HSD at the EDS Clinic using the 2017 diagnostic criteria, we found that 66.5% ($n=1389$) were diagnosed with HSD, 20.3% ($n=423$) with hEDS, 10.6% ($n=256$) were not diagnosed with hEDS or HSD but included patients with H-HSD and L-HSD (hypermobile controls) and 2.6% ($n=55$) were not diagnosed with hEDS, HSD, H-HSD or L-HSD (controls).

Demographic data were not significantly different between the HSD, hEDS or control groups for age ($P=0.141$), race ($P=0.250$) or highest level of education ($P=0.267$) (Table 2). Each group was comprised mainly of females: HSD 93.2%, hEDS 93.2% and controls 83.6% (Table 2). Around 90% of patients from each group were White and >87% for each diagnosis identified as non-Hispanic (Table 2). The median age was similar for patients with HSD (33.8 years), hEDS (34.8 years) and controls (36.6 years) ($P=0.141$). However, we found that 'hypermobile controls' were significantly older than patients with hEDS or HSD (hypermobile controls 38.3 years, hEDS 33.9 years, HSD 32.0 years; $P=0.0001$). This was one of the reasons we did not use the 'hypermobile control' group for the study.

The states of residence of the patients are found in Supplementary Table S1, available at *Rheumatology Advances in Practice* online. There was no significant difference between controls, hEDS or HSD for self-reported smoking, illicit drug use or alcohol use except for alcohol

Table 1. List of symptoms/comorbidities that differ between controls

Characteristics	Control (no hEDS, HSD, H-HSD or L-HSD) ($n = 55$)	'Hypermobile' control (no hEDS or HSD) ($n = 221$)	*P*-value (or borderline significant)[a]
Age, years, median (S.D.)	36.6 (13.6)	39.6 (15.0)	0.217
BMI, median (S.D.)	24.3 (5.1)	27.0 (9.3)	0.041
Joint problems, *n* (%)			
Joint pain	32 (58.2)	178 (80.5)	0.0005
Subluxations	7 (12.7)	123 (55.7)	<0.0001
Dislocations	2 (3.6)	46 (20.8)	0.003
Sprains	9 (16.4)	111 (50.2)	<0.0001
TMJ symptoms	10 (18.2)	73 (33.0)	0.032
Neurological, *n* (%)			
New daily persistent headache	16 (29.1)	39 (17.6)	0.057
Brain fog	26 (47.3)	143 (64.7)	0.018
Cold intolerance	13 (23.6)	87 (39.4)	0.030
Heat intolerance	12 (21.8)	79 (35.7)	0.049
Sleep, *n* (%)			
Insomnia	11 (20.0)	78 (35.3)	0.030
Sleep disturbances	7 (12.7)	83 (37.6)	0.0004
GI, *n* (%)	234 (91.4)	212 (90.6)	
Pain/cramps in lower abdomen	27 (49.1)	76 (34.4)	0.044
Dyspepsia (heartburn)	8 (14.5)	66 (29.9)	0.022
Haemorrhoids	8 (14.5)	59 (26.7)	0.060
Faecal incontinence (leakage of faeces)	0 (0.0)	15 (6.8)	0.047
Rectal prolapse	0 (0.0)	11 (5.0)	0.091
How long have you had these GI symptoms (years)?, median (S.D.)	9.2 (8.1)	39.9 (219.3)	0.006
Allergy/asthma, *n* (%)			
Asthma as an adult	5 (9.1)	45 (20.4)	0.052
Wheezing	1 (1.8)	25 (11.3)	0.031
Hives	3 (5.5)	35 (15.8)	0.046
Psychological, *n* (%)			
Anxiety	24 (43.6)	127 (57.5)	0.065
Bipolar	0 (0.0)	12 (5.4)	0.077
Central sensitization, *n* (%)			
Possible diagnosis for central sensitization	24 (60.0)	123 (79.4)	0.011
Percent positive answers, median (S.D.)	44.5 (21.2)	56.0 (19.4)	0.002

[a] *P*-values result from Fisher's test for categorical data and Kruskal–Wallis rank sum test for numeric data.

consumption ($P = 0.041$) (Yes, current drinker: controls 24.3%, HSD 27.3%, hEDS 26.1%) and BMI (controls 47.3%, HSD 51.5%, hEDS 56.8%) ($P < 0.0001$) (Supplementary Table S2, available at *Rheumatology Advances in Practice* online). However, patients with HSD had a significantly higher BMI than patients with hEDS ($P < 0.0001$).

Joint pain, muscle weakness and bruising

Joint pain ($P < 0.0001$), subluxations ($P < 0.0001$), sprains ($P < 0.0001$), easy bruising ($P < 0.0001$), muscle weakness ($P < 0.0001$), temporomandibular joint symptoms ($P < 0.0001$), and dislocations ($P < 0.0001$) were all self-reported more often in patients with hEDS or HSD compared with controls (Supplementary Table S3, available at *Rheumatology Advances in Practice* online). Most patients (>50%) with a diagnosis of hEDS or HSD self-reported symptoms of joint pain, subluxations and joint concerns like sprains (Supplementary Table S4, available at *Rheumatology Advances in Practice* online). Patients diagnosed with HSD self-reported significantly more symptoms, including joint pain ($P = 0.002$), easy bruising ($P < 0.0001$), muscle weakness ($P < 0.0001$) and TMJ symptoms ($P < 0.0001$) than those with hEDS (Supplementary Table S4, available at *Rheumatology Advances in Practice* online; Fig. 1A). In contrast, patients diagnosed with hEDS self-reported significantly more dislocations ($P = 0.0008$) than patients with HSD (Supplementary Table S4, available at *Rheumatology Advances in Practice* online; Fig. 2).

Teeth/oral symptoms and comorbidities

The presence of a high or narrow palate ($P = 0.005$), TMJ symptoms ($P < 0.0001$) and brittle teeth ($P = 0.019$) were all self-reported more often in patients with hEDS or HSD compared with controls, with overcrowding being borderline significant ($P = 0.056$) (Supplementary Table S5, available at *Rheumatology Advances in Practice* online). We found that a high and narrow palate was reported more often in patients with hEDS compared with HSD ($P = 0.016$) (Supplementary Table S6, available at *Rheumatology Advances in Practice* online; Fig. 2), as expected, as it forms part of the diagnostic criteria for distinguishing hEDS from HSD [4]. Patients with hEDS also self-reported more overcrowding ($P = 0.033$) and brittle teeth ($P = 0.031$) than patients with HSD (Supplementary Table S6, available at *Rheumatology Advances in Practice* online; Fig. 2). The only teeth/oral symptom that was self-reported more often in patients with HSD compared with those with hEDS was TMJ symptoms ($P < 0.0001$) (Fig. 1A).

Asthma, allergy and related symptoms

We examined whether patients self-reported mast cell symptoms/conditions such as asthma and related chest symptoms, allergy/atopy or other hypersensitivity symptoms on the

Table 2. Demographics of patients diagnosed at the EDS Clinic ($n = 1867$)

Characteristics	Controls ($n = 55$)	HSD ($n = 1389$)	hEDS ($n = 423$)	*P*-value[a]
Age, years, median (S.D.)	36.6 (13.6)	33.8 (12.3)	34.8 (12.1)	0.141
Sex, *n* (%)				0.0001
Female	46 (83.6)	1295 (93.2)	374 (88.4)	
Male	9 (16.4)	67 (4.8)	44 (10.4)	
Non-binary	0 (0.0)	23 (1.7)	4 (0.9)	
Other	0 (0.0)	4 (0.3)	1 (0.2)	
Race, *n* (%)				0.250
American Indian/Alaskan native	0 (0.0)	19 (1.5)	8 (2.2)	
Asian	2 (3.6)	24 (1.8)	1 (0.3)	
Black or African American	3 (5.5)	26 (2.0)	11 (3.0)	
Native Hawaii/Pacific Islander	0 (0.0)	2 (0.2)	0 (0.0)	
White	48 (87.3)	1197 (91.8)	337 (91.6)	
Other	1 (1.8)	25 (1.9)	5 (1.4)	
Unknown/not disclosed	1 (1.8)	11 (0.8)	6 (1.6)	
Ethnicity, *n* (%)				0.011
Hispanic or Latino	5 (9.1)	103 (7.9)	20 (5.4)	
Not Hispanic or Latino	45 (81.8)	1169 (89.6)	341 (92.7)	
Unknown/not disclosed	5 (9.1)	32 (2.5)	7 (1.9)	
Highest level of education, *n* (%)				0.267
Some high school	3 (5.5)	59 (4.5)	5 (1.4)	
High school/GED	4 (7.3)	110 (8.5)	24 (7.0)	
Some college	9 (16.4)	287 (22.1)	83 (24.1)	
Trade school	0 (0.0)	60 (4.6)	14 (4.1)	
Associate's degree	4 (7.3)	147 (11.3)	45 (13.0)	
Bachelor's degree	18 (32.7)	384 (29.6)	98 (28.4)	
Master's degree	11 (20.0)	179 (13.8)	53 (15.4)	
Professional/doctorate	5 (9.1)	65 (5.0)	21 (6.1)	
Not disclosed	1 (1.8)	7 (0.5)	2 (0.6)	

[a] *P*-values result from Fisher's test for categorical data and Kruskal–Wallis rank sum test for numeric data.

intake questionnaire. We found that allergy/atopy was high in all three groups and was similar between patients diagnosed with hEDS or HSD (77%, $P = 0.604$) (Supplementary Tables S7 and S8, available at *Rheumatology Advances in Practice* online). Controls had significantly fewer allergy/asthma symptoms for almost all examined conditions (Supplementary Table S7, available at *Rheumatology Advances in Practice* online). Asthma occurred in ≈20% of adults with hEDS or HSD ($P = 0.808$) (Supplementary Table S8, available at *Rheumatology Advances in Practice* online). Palpitations ($P < 0.0001$), multiple sensitivities ($P < 0.0001$), chest discomfort ($P < 0.0001$), shortness of breath ($P = 0.0001$), sun sensitivity ($P < 0.0001$), rash ($P = 0.026$), hives ($P = 0.027$) and oral ulcers ($P = 0.011$) were self-reported significantly more often in patients with HSD than those with hEDS (Supplementary Table S8, available at *Rheumatology Advances in Practice* online; Fig. 1B). Asthma as a child was also reported more often in patients with HSD than hEDS and was borderline significant ($P = 0.061$).

Neurological symptoms and comorbidities

The neurological conditions that we examined are listed according to the greatest percentage reported in patients with HSD in Supplementary Table S9, available at *Rheumatology Advances in Practice* online. We have listed some items in more than one table, with the idea that the symptom or comorbidity may have more than one cause or symptom association and thus fit into more than one category, and it is helpful to consider them together with other symptoms. Additionally, some of the symptoms listed here can have multiple causes, with a neurological explanation being only one possibility. Most of the neurological conditions that we assessed were significantly increased in patients with hEDS or HSD compared with controls (Supplementary Table S9, available at *Rheumatology Advances in Practice* online). Around 70% of patients diagnosed with hEDS or HSD self-reported experiencing brain fog and headache (Supplementary Table S10, available at *Rheumatology Advances in Practice* online). Except for autonomic dysfunction ($P = 0.022$), delay in developmental milestones ($P = 0.048$) and abnormal brain MRI ($P = 0.044$), which were self-reported more often in patients with hEDS, all other self-reported neurological conditions that were significantly different between groups were reported more often in patients with HSD compared with hEDS (Supplementary Table S10, available at *Rheumatology Advances in Practice* online; Fig. 2). Neurological symptoms self-reported more often in patients with HSD included light-headedness ($P < 0.0001$), numbness/tingling of the extremities ($P < 0.0001$), pain/cramps in the lower abdomen ($P < 0.0001$), sense of imbalance ($P < 0.0001$), heat intolerance ($P < 0.0001$), palpitations ($P < 0.0001$), cold intolerance ($P = 0.003$), multiple sensitivities (e.g. lights, smells, foods, medicine) ($P < 0.0001$), ringing in the ears ($P < 0.0001$), blurred vision ($P = 0.0007$), dry eyes ($P = 0.0009$), increased sweating ($P < 0.0001$), new daily persistent headache ($P = 0.019$), dry mouth ($P = 0.0003$), hearing difficulties ($P = 0.005$) and loss or change of taste ($P = 0.019$) (Supplementary Table S10, available at *Rheumatology Advances in Practice* online; Fig. 1C).

Headache and migraine

The percentage of headache and/or migraine self-reported by patients with hEDS or HSD were quite similar (Fig. 3).

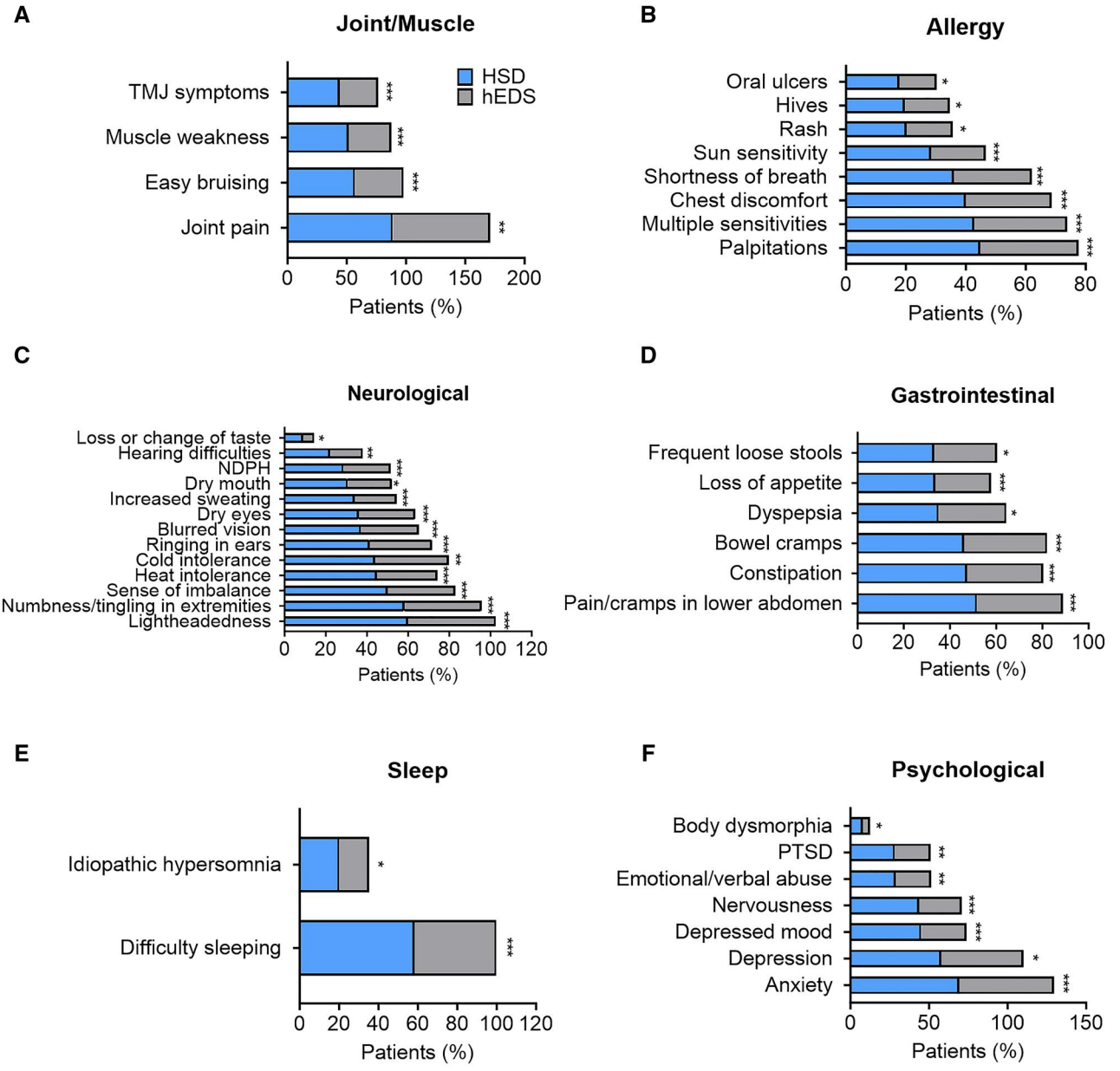


Figure 1. Symptoms/comorbidities self-reported more often in patients diagnosed with HSD. Order based on percentage of comorbidity in HSD. **(A)** Joint/muscle: joint pain ($P = 0.002$), easy bruising ($P < 0.0001$), muscle weakness ($P < 0.0001$), TMJ symptoms ($P < 0.0001$); **(B)** allergy: palpitations ($P < 0.0001$), multiple sensitivities ($P < 0.0001$), chest discomfort ($P < 0.0001$), shortness of breath ($P = 0.0001$), sun sensitivity ($P < 0.0001$), rash ($P = 0.026$), hives ($P = 0.027$), oral ulcers ($P = 0.011$); **(C)** neurological: light-headedness ($P < 0.0001$), numbness/tingling of the extremities ($P < 0.0001$), sense of imbalance ($P < 0.0001$), heat intolerance ($P < 0.0001$), cold intolerance ($P = 0.003$), multiple sensitivities (e.g. lights, smells, foods, medicine) ($P < 0.0001$), ringing in the ears ($P < 0.0001$), blurred vision ($P = 0.0007$), dry eyes ($P = 0.0009$), increased sweating ($P < 0.0001$), new daily persistent headache (NDPH) ($P = 0.019$), dry mouth ($P = 0.0003$), hearing difficulties ($P = 0.005$), loss or change of taste ($P = 0.019$); **(D)** gastrointestinal: pain/cramps in the lower abdomen ($P < 0.0001$), diarrhoea ($P = 0.015$), bowel cramps ($P < 0.0001$), dyspepsia ($P = 0.029$), loss of appetite ($P = 0.0002$), frequent loose stools ($P = 0.022$); **(E)** sleep: difficulty falling and staying asleep ($P < 0.0001$), idiopathic hypersomnia ($P = 0.019$); **(F)** psychological: anxiety ($P = 0.0006$), depression ($P = 0.036$), depressed mood ($P < 0.0001$), nervousness ($P < 0.0001$), emotional/verbal abuse ($P = 0.008$), post-traumatic stress disorder (PTSD) ($P = 0.009$), body dysmorphic disorder ($P = 0.032$); $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

Around 70% of patients diagnosed with hEDS or HSD self-reported experiencing headache, followed by migraine at >50% (Supplementary Table S10, available at *Rheumatology Advances in Practice* online; Fig. 3). New daily persistent headache ($P = 0.019$) was self-reported more often in patients diagnosed with HSD and cluster headache was borderline significant ($P = 0.050$) (Supplementary Table S10, available at *Rheumatology Advances in Practice* online; Fig. 3).

GI symptoms

Patients in this study self-reported that they had GI symptoms for ≈33 years for HSD and 48 years for hEDS compared with 9 years for controls ($P = 0.005$) (Supplementary Table S11, available at *Rheumatology Advances in Practice* online). The difference in years that hEDS and HSD patients experienced stomach and intestinal symptoms was not significantly different ($P = 0.534$) (Supplementary Table S12, available at *Rheumatology Advances in Practice* online). Most symptoms

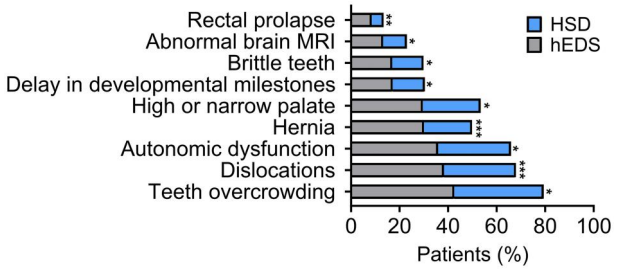


Figure 2. Symptoms/comorbidities self-reported more often in patients diagnosed with hEDS. Order based on percentage of condition in hEDS. Symptoms/comorbidities include dislocations ($P = 0.0008$), high or narrow palette ($P = 0.016$), teeth overcrowding ($P = 0.033$), brittle teeth ($P = 0.031$), autonomic dysfunction ($P = 0.022$), delay in developmental milestones ($P = 0.048$), abnormal brain MRI ($P = 0.044$) and rectal prolapse ($P = 0.005$). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$

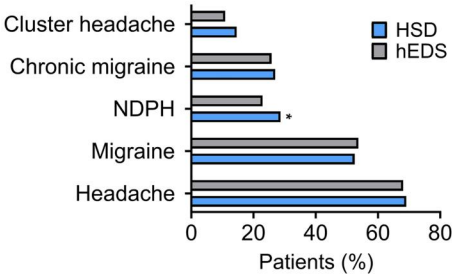


Figure 3. Self-reported headache and migraine similar in hEDS and HSD patients. Order is based on percentage of condition in HSD. NDPH: new daily persistent headache. $^{*}P < 0.05$

examined in this study were self-reported more often in patients with hEDS and HSD compared with controls (Supplementary Table S11, available at *Rheumatology Advances in Practice* online). All the GI symptoms (Supplementary Table S12, available at *Rheumatology Advances in Practice* online) that were significantly different between patients with HSD and hEDS were reported more often in patients with HSD except for rectal prolapse, which was reported more often in patients with hEDS ($P = 0.005$) (Supplementary Table S12, available at *Rheumatology Advances in Practice* online; Fig. 1D, Fig. 2). Haemorrhoids were also self-reported more in patients with hEDS, which was borderline significant ($P = 0.062$). GI symptoms that were reported more often in patients with HSD compared with hEDS included pain/cramps in the lower abdomen ($P < 0.0001$), diarrhoea ($P = 0.015$), bowel cramps ($P < 0.0001$), dyspepsia ($P = 0.029$), loss of appetite ($P = 0.0002$) and frequent loose stools ($P = 0.022$) (Supplementary Table S12, available at *Rheumatology Advances in Practice* online; Fig. 1D).

Sleep symptoms and comorbidities

In this study we found that patients with hEDS or HSD self-reported more symptoms of difficulty falling and staying asleep ($P < 0.0001$), insomnia ($P = 0.005$) and sleep disturbances ($P = 0.0002$) than controls (Supplementary Table S13, available at *Rheumatology Advances in Practice* online). Comparing hEDS with HSD, patients diagnosed with HSD self-reported having difficulty falling and staying asleep ($P < 0.0001$) and idiopathic hypersomnia ($P = 0.019$) more often than those with hEDS (Supplementary Table S14, available at *Rheumatology Advances in Practice* online; Fig. 1E).

Psychological conditions and abuse

In this study, patients with hEDS or HSD did not self-report autism/autism spectrum disorder (ASD) more frequently than controls ($P = 0.250$) (Supplementary Table S15, available at *Rheumatology Advances in Practice* online). Only ≈5–7% of patients diagnosed with hEDS or HSD self-reported having ASD (Supplementary Table S15, available at *Rheumatology Advances in Practice* online).

We found that patients diagnosed with hEDS or HSD self-reported a number of psychological symptoms more often than controls, including anxiety ($P < 0.0001$), depression ($P = 0.0002$), depressed mood ($P < 0.0001$), nervousness ($P < 0.0001$), emotional/verbal abuse ($P = 0.002$), post-traumatic stress disorder (PTSD) ($P = 0.009$) and attention deficit disorder (ADD)/attention deficit hyperactivity disorder (ADHD) ($P = 0.020$) (Supplementary Table S15, available at *Rheumatology Advances in Practice* online). Comparing hEDS with HSD, patients with HSD self-reported more anxiety ($P = 0.0006$), depression ($P = 0.036$), depressed mood ($P < 0.0001$), nervousness ($P < 0.0001$), emotional/verbal abuse ($P = 0.008$), PTSD ($P = 0.009$) and body dysmorphic disorder ($P = 0.032$) than patients with hEDS (Supplementary Table S16, available at *Rheumatology Advances in Practice* online; Fig. 1F). Physical abuse was borderline increased in patients with HSD compared with hEDS ($P = 0.066$).

Similarities in patients with hEDS and HSD

Self-reported symptoms and comorbidities that occurred at a similar percentage in patients diagnosed with hEDS or HSD in this study included joint pain (80%), allergy (77%), subluxations (70%), brain fog (70%), headache (68%), anxiety and depression (50–60%) and migraine, nausea and constipation (50% each). Symptoms and comorbidities that were not significantly different between patients with hEDS and HSD included allergies/atopy (77%), subluxations (70%), headache (68%), sprains (65%), constipation (53%), migraine (52%), tinnitus (45%), gastroesophageal reflux disease (40%), insomnia and sleep disturbances (38%), vertigo (34%), history of abuse (33%), irritable bowel syndrome (32%), ADD/ADHD (25%), chronic migraine (25%), neuropathy (24%), asthma/wheezing (20%), snoring and sleep apnoea (8%) and autism (5%) (Fig. 4).

Discussion

In this study we found that there were several self-reported symptoms/comorbidities that occurred in a similar percentage of patients with hEDS or HSD, such as allergies, subluxations, sprains, headache and migraine. Most of the symptoms/comorbidities that were examined occurred in both patient groups. However, there were significant differences between some conditions by diagnosis, suggesting that there may be distinct differences between the two diagnoses. For example, patients diagnosed with HSD reported 42 conditions more often compared with hEDS [42/115 (37%)], while only 9 conditions occurred more often in patients with hEDS [9/115 (8%)]. Additionally, we found that all allergy conditions that were significantly different were self-reported more often in patients with HSD than hEDS. Another important finding was that the conditions reported more often in hEDS were ‘structural’ whereas conditions reported more often in HSD were ‘functional’. We previously published that patients

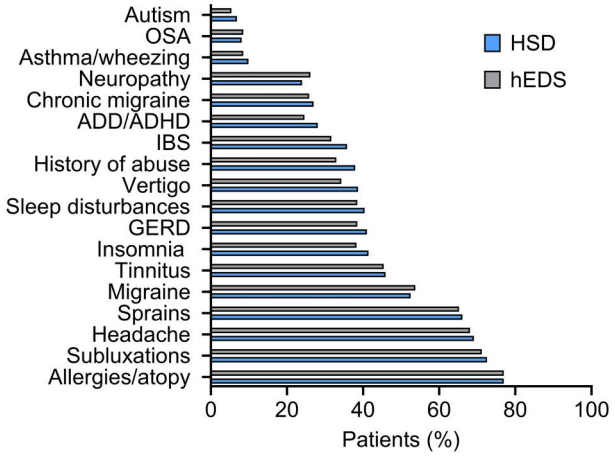


Figure 4. Symptoms/comorbidities that similarly effect patients diagnosed with hEDS and HSD. Order based on percentage of condition in HSD. No significant differences were found in symptoms/comorbidities listed in this figure between patients with a diagnosis of hEDS *vs* HSD. GERD: gastroesophageal reflux disease; IBS: irritable bowel syndrome; OSA: obstructive sleep apnoea

diagnosed with hEDS or HSD and fibromyalgia self-reported more symptoms/comorbidities, suggesting that severity may be indicated more by an overlap with fibromyalgia than a diagnosis of hEDS or HSD itself [7].

Several other studies have compared symptoms and comorbidities in patients diagnosed with hEDS or HSD since the new diagnostic criteria were established in 2017. A study by Copetti *et al.* [8] examined 105 patients diagnosed with hEDS or HSD for 59 characteristics and analysed data using hierarchical clustering of principal components. They found that some patients within both diagnoses were considered more severe regardless of the diagnosis and recommended a new severity score. However, they did not specifically examine or report which of their patients were also diagnosed with fibromyalgia or how that related to their score. Previously we reported that 56% of patients diagnosed with hEDS or HSD were also diagnosed with fibromyalgia, and patients who had both diagnoses had more symptoms/comorbidities, suggesting that they were more 'severe' than patients diagnosed with only hEDS or HSD [7]. Thus Copetti *et al.*'s [8] findings appear to have a conclusion similar to ours, although it is difficult to compare the two studies directly because of different methods of data analysis. In a study by Aubry-Rozier *et al.* [14], 97 patients (61 hEDS, 36 HSD) were diagnosed at their specialty clinic with hEDS or HSD and given the 16-item Clinical Severity Score (CSS-16) questionnaire. They found that 82% of patients reported pain and >40% reported fatigue, sleep disturbance, dysautonomia, mast cell activation and GI symptoms. They found that CSS-16 questionnaire scores were significantly higher for patients diagnosed with hEDS compared with HSD, but among the 16 symptoms/comorbidities examined only pain, motor and bleeding problems were significantly more severe in hEDS compared with HSD patients. It is difficult to compare this study with ours because of the low number of HSD patients and a different evaluation method. A study by McGillis *et al.* [15] compared hEDS and HSD patients based on the 2017 diagnostic criteria (20 hEDS *vs* 111 HSD, although only 90 HSD by the 2017 criteria) for orthostatic intolerance, postural orthostatic tachycardia syndrome, mast cell activation syndrome, headache/migraine, psychological comorbidities and GI dysfunction. They did not find a significant difference between diagnoses for any symptom/comorbidity, although they examined a relatively small number of patients. A similar finding was observed by Martinez *et al.* [10], who also studied a relatively small number of patients (98 hEDS and 27 HSD). Additionally, an oral abstract submitted to the Ehlers-Danlos Society 2022 International Scientific Symposium on EDS and HSD reported their initial analysis of the worldwide Ehlers–Danlos Society registry that examined 8867 hEDS and 990 HSD patients for eight symptoms/comorbidities, including fatigue, GI symptoms, headache, anxiety, depression, dysautonomia, gynae, bladder and mast cell activation disease [12]. They did not find any differences in these eight categories of self-reported symptoms/comorbidities between patients with hEDS or HSD. However, the published abstract does not provide information on whether all patients were diagnosed using the 2017 criteria or information on race/ethnicity or statistics. One possible explanation for the differences in our findings compared with the initial reports from the Ehlers–Danlos Society registry is that our population is almost 90% White non-Hispanic and their study includes many races/ethnicities.

Another recent study examined 94 patients diagnosed with hEDS and 80 with HSD from Italy and the USA using the 2017 diagnostic criteria compared with healthy controls ($n = 129$) [11]. They compared self-reported symptoms/comorbidities including GI, neurological, psychological, bladder/urological, gynaecological, chronic fatigue, TMJ and allergy/atopy between the two diagnoses. They found that patients with hEDS self-reported significantly more chronic fatigue, functional GI, neurological and allergy/atopy symptoms/comorbidities than patients with HSD. Although they had different results than ours, their findings also suggest important differences between the two diagnoses. Their cohort was primarily Italian, raising the possibility that race/ethnicity may influence the data. Compared with these studies, our study is the largest to date with a clearly defined patient diagnosis and comparison with a control group that is not diagnosed with hypermobility.

There are several limitations to the current study. The site of this study is a tertiary care centre and findings from patients in this study may not represent other regions of the USA or world. Additionally, symptoms/comorbidities were self-reported and not validated through another method. Future studies are needed to examine whether the key findings of this study can be verified when medical records are examined. This is critical because several issues examined need clarification, such as whether self-reported headache could be migraine or other primary headache disorders as defined by the international classification of headache disorders or whether patients self-diagnosed because of certain symptoms they were experiencing. A strength of this study is that hEDS/HSD patients were diagnosed using the most recent 2017 criteria by physician experts. An additional strength is the large study population that contained an internal control group, which was not diagnosed with hEDS, HSD, H-HSD or L-HSD but had the same diagnostic process. The significantly higher levels of joint and other symptoms found in the 'hypermobile control' patients suggests that future studies should examine whether patients with H-HSD and L-HSD have significant symptoms/comorbidities that also need to be addressed.

These findings indicate that high overlap exists in symptoms and comorbidities in both diagnoses, but distinct differences also exist. A future question that needs to be addressed is whether these quantitative differences equate to qualitative differences in patient experience. Gaining a better understanding of the differences between patients with hEDS and HSD may improve patient care and provide mechanistic insights into similarities and differences in the pathogenesis of disease. Research into these mechanisms may lead to improved tailored therapies that reduce the progression of disease.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

The data are presented within the manuscript and supplemental materials.

Authors' contributions

D.F., D.K. and K.B. designed the study. D.K. and S.G. diagnosed the hEDS/HSD and fibromyalgia patients. A.D., D.F., E.W., A.J. and K.B. built and/or managed the electronic database of patient data. A.D., S.C.K., J.F., S.K., G.W., E.M. and V.B. collected data. A.D., M.B., D.F., S.C.K., D.K. and K.B. analysed the data. A.D., M.B., D.F., S.C.K., D.K., F.F. and K. B. interpreted the data. A.D. and D.F. wrote the manuscript. D.F., D.K. and K.B. agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy and integrity of any part of the work are properly investigated and resolved. All authors interpreted the data, edited and revised the article and approved the final version of the article.

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