The Spider; A Multisystemic Symptom Impact Tool for People with Hypermobility-Related Disorders. Initial Validation in Adolescents

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Objectives The multisystemic comorbid symptoms/conditions of hypermobility spectrum disorders (HSD) and hypermobile Ehlers-Danlos syndrome (hEDS) often significantly affect daily life. Many of these symptoms are under-recognized during diagnosis and treatment; therefore, a comprehensive questionnaire was developed to evaluate their presence and impact. The Spider's 8 domains assess neuromusculoskeletal, pain, fatigue, cardiac dysautonomia, urogenital, gastrointestinal, anxiety, and depression symptoms. This study aims to evaluate the construct validity of the Spider in adolescents.

Study design This cross-sectional study recruited international participants through 3 patient charities and a hypermobility unit. Adolescents aged 13-18 years, with and without HSD/hEDS, were included. Validated and frequently used comparator questionnaires were used to establish convergent validity. Participants answered each Spider domain and the respective comparator via 4 online surveys. Convergent validity was assessed by comparing Spider domain and comparator scores through correlational analysis. Known-group validity was assessed by comparing Spider domain scores of hypermobile and control groups using Mann-Whitney *U* analysis.

Results In total, 1154 adolescents participated, 1036 with HSD/hEDS and 118 controls. Six domains (pain, fatigue, depression, cardiac dysautonomia, gastrointestinal, and neuromusculoskeletal) demonstrated strong correlations ($r = -0.7$ to 0.8) with the respective comparator. The urogenital and anxiety domains showed moderate correlations ($r = 0.6$). All correlations reached statistical significance ($P < .001$). Known-group validity was demonstrated in 7 domains ($P < .001$). The urogenital domain did not show a significant difference between the groups ($P = .094$).

Conclusions The Spider domains demonstrate acceptable convergent validity. The Spider questionnaire can accurately, rapidly, and concisely measure the effect of common multisystemic comorbid symptoms/conditions associated with HSD/hEDS to help direct care in adolescents. *(J Pediatr 2024;12:200098)*.

Joint hypermobility (JH) describes an increased active and passive range of joint motion, locally or generally. JH is a spectrum, with age, sex assigned at birth, and ethnicity influencing normal joint range.[1] Although some individuals with JH remain asymptomatic, others experience complex and varied multisystemic comorbid symptoms/conditions. Historically, various terms have been used to describe individuals with symptomatic JH; however, in 2017, the International Ehlers Danlos Syndrome (EDS) consortium refined diagnostic criteria and recommended the use of the terms "hypermobility spectrum disorder" (HSD)[2] and "hypermobile Ehlers Danlos syndrome" (hEDS).[3] HSD and hEDS have been described on a continuum as largely overlapping conditions with similarities in symptom presentation and management strategies.[2]

CALI-9	Child Activity Limitations Interview-9	MFS	Multidimensional Fatigue Scale
BIoH	Bristol Impact of Hypermobility questionnaire	NMSK	Neuromusculoskeletal
CI	Confidence Intervals	Peds-QL	Pediatric Quality of Life Inventory
DVSS	Dysfunctional Voiding Scoring System	Peds-QL GIS	Pediatric Quality of Life Inventory GastroIntestinal Scales
EDS	Ehlers Danlos syndrome	PinQ	Pediatric incontinence Questionnaire
GJH	Generalized Joint Hypermobility	PROM	Patient-reported outcome measure
hEDS	hypermobile Ehlers Danlos syndrome	PROMs	Patient reported outcome measures
HSD	Hypermobility spectrum disorders	RCADS-25	Revised Child Anxiety and Depression Scale
JH	Joint hypermobility	SH	Symptomatic hypermobility

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The prevalence of HSD/hEDS is difficult to ascertain but appears to be greater than previously thought. Although the overall reported prevalence of EDS types is between 1 in 3100 and 1 in 5000,[4,5] a United Kingdom-based study reported the prevalence of HSD/hEDS to be 194.2 per 100 000, or approximately 10 cases per 5000 patients.[6] It may be 1000 times more common than rheumatoid arthritis and nearly as prevalent as fibromyalgia.[7] In the United Kingdom, adults with hypermobility reportedly make up 30% of patients in primary care clinics, 39% of those in pain management, and 37% of those seen by rheumatologists.[8] Reports suggest that prevalence in children and young people ranges between 5% and 65%,[9] the variation attributable to age, sex assigned at birth, ethnicity, and diagnostic criteria used.[4,5,7-10]

In addition to the commonly recognized musculoskeletal symptoms, evidence continues to report that HSD/hEDS is associated with multisystemic comorbid symptoms/conditions.[2] Comorbid symptoms of orthostatic intolerance, fatigue, difficulties with gastrointestinal and urological systems, as well as anxiety and depression often are reported alongside neuromusculoskeletal symptoms.[11] These symptoms can vary in prevalence and severity, leading to diverse clinical presentations. The clinical characteristics of adolescents with HSD/hEDS were identified in a scoping review of 54 studies.[12] Musculoskeletal characteristics (joint instability and pain) were reported in 85% of studies, cardiovascular characteristics (including orthostatic intolerance) in 37%, fatigue in 24%, gastrointestinal characteristics (including diarrhea and constipation) in 22%, urogenital characteristics (such as incontinence and recurrent bladder infections) in 15%, and psychosocial features (including anxiety and depression) in 11% of studies. Clinician awareness of these comorbid symptoms/conditions and their effect is crucial for individualized care and management, as they can greatly affect function and daily living and quality of life if overlooked.[2] Despite the prevalence of people with HSD/hEDS in clinical settings and the growing body of evidence, the multisystemic nature of these conditions is poorly recognized. Russek et al assessed American clinicians' knowledge of JH and reported that only 24% regarded HSD/hEDS as multisystemic and 4.4%-18.9% recognized associated comorbidities such as fatigue, anxiety, and bowel disorders.[13] This highlights a gap in clinician knowledge that may lead to poorly managed symptoms, as demonstrated by a study reporting that 99% of participants with HSD/hEDS had unmet medical needs.[14] Evidence suggests that individuals reporting multisystemic symptoms may have a worse health status and prognosis.[15] Some may not realize that their nonmusculoskeletal symptoms are more common in HSD/hEDS, so unless directly questioned about these, important information may be missed and symptoms left untreated.[7] Awareness of these symptoms and their effects by both clinicians and patients is imperative for early individualized care and management.

To improve insight into the symptom profile of individuals with HSD/hEDS, "The Spider" questionnaire tool was developed to evaluate and help visualize the presence and effect of 8 commonly associated multisystemic comorbid symptoms/conditions. This study presents the initial validation process of the Spider domains in an adolescent population with the aim of establishing construct validity.

Methods

The Spider Questionnaire

The Spider is a screening tool designed to recognize the presence and impact of comorbid symptoms/conditions, to identify areas of need for treatment and follow-up, and to direct holistic care and management. It comprises 31 items in 8 domains assessing multisystemic comorbid symptoms/conditions associated with HSD/hEDS: pain, fatigue, neuromusculoskeletal, cardiac dysautonomia, urogenital, gastrointestinal, anxiety, and depression (**Appendix**, online; available at www.jpeds.com). The scoring system uses a 6-point Likert scale, with "not present" and "no impact on daily life" scoring 0, and "mild," "moderate," "severe," and "disabling" impact scoring 25, 50, 75, and 100, respectively. Two questions have alternative scoring (q.19 and q.25) scored between 0 and 100. Individual domains are scored by averaging the total score of domain questions, providing an overall domain percentage, with greater scores indicating greater impact on daily living. The completed Spider questionnaire produces a radar graph, providing a visual overview of a patient's symptom profile (**Figure 1**).

Team of Experts. The Spider questionnaire was developed by an international research group, including researchers and clinicians from University College London, Ghent University Hospital, Imperial College London, and Johns Hopkins University. The team included a consultant rheumatologist, 2 pediatricians, 6 pediatric physiotherapists, and a statistician. This multidisciplinary team specializes in diagnosis and treatment of patients with hypermobility and is active in research regarding HSD/hEDS and heritable connective tissue disorders.

Initial Development, Face, and Content Validity. The COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist was used to guide development of the Spider.[16] The initial draft comprised 10 axes ("spider legs") with 60 questions based on clinical experience, previous research in HSD/hEDS, and the common data environment established by the Allied Health Practitioners working group of the International EDS Society. Initial content and face validity were established in 2019, led by one of the authors (I.D.W.). The selection, content, and wording of the questions; the domain construct and scoring; and the questionnaire's relevance and comprehensiveness were reviewed by 3 additional international hypermobility experts selected from the International EDS Consortium. After feedback, 2 axes ("cognitive deficits" and "allergy and mast cell activation") were removed. Cognitive impairment was examined within the fatigue and mental health domains, and there was insufficient evidence supporting the association of mast cell activation and HSD/hEDS.[17] Initially, a 5-part Likert scale

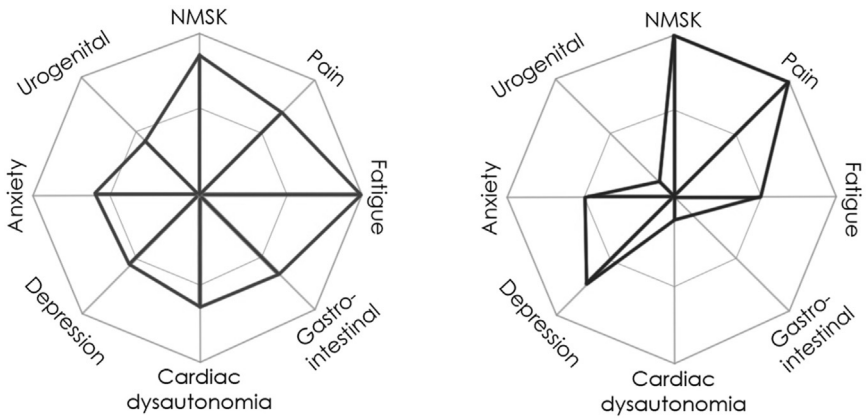

Figure 1. An example of 2 completed questionnaire radar graphs. Greater scores, and therefore greater impact, are plotted toward the edges of the radar graph. *NMSK*, neuromusculoskeletal.

was agreed, and the number of questions was reduced to 25. Further face and content validity and clinical utility was evaluated by piloting the second version of the Spider in 172 adolescents and adults with HSD/hEDS. Participant feedback on the included questions and domains resulted in the wording in several items being adjusted (eg, "anxiety" changed to "worry") and the number of questions increased to 31. In 2021, a "not present" option was introduced to differentiate between symptoms that were present but not significantly impacting daily life and absent symptoms.

Construct Validity. Although the Spider is designed for use with adolescents and adults, this first validation study focused on adolescents. The aim of this work was to establish construct validity through convergent and known-group validity analysis using a cross-sectional research design. Ethical approval was granted by the University College London Research Ethics Committee (19629/001). The 4 study stages were completed between 2020 and 2022 to ensure effective recruitment and minimize participant fatigue. Convergent validity was measured by correlating each Spider domain with existing validated questionnaires measuring similar constructs. The most appropriate validated comparator patient-rated outcome measures (PROMs) were chosen based on their concepts and psychometric properties, including validity, reliability, and clinical utility. Known-group validity was explored to determine whether each Spider domain could differentiate between a group of individuals with symptomatic hypermobility (SH) and nonhypermobile controls.

- Stage 1, 2020: The construct validity of the Spider pain and fatigue domains was assessed using The Pediatric Quality of Life (Peds-QL) Multidimensional Fatigue Scale (MFS)[18] and the Child Activity Limitations Interview-9 (CALI-9)[19] as comparators.
- Stage 2, 2021: The construct validity of the anxiety and depression domains was assessed using the Revised Child Anxiety and Depression Scale-25 (RCADS-25)[20] as a comparator.
- Stage 3, 2022: The construct validity of the urogenital, cardiac dysautonomia, and the neuromusculoskeletal domains was assessed using the Dysfunctional Voiding Scoring System (DVSS),[21] the COMPASS-31,[22] and the Bristol Impact of Hypermobility questionnaire (BIoH).[23] Only the orthostatic domain of the COMPASS-31 was used, as the other COMPASS-31 questions analyzed areas of autonomic dysfunction which were irrelevant to this domain. As there is no discriminate measure that assesses the neuromuscular symptoms associated with hypermobility, questions 10 to 16 from section D and questions 48, 51, 52, and 53 from section I from the BIoH were used with permission and advice from its creators.
- Stage 4, 2022: The construct validity of the gastrointestinal domain was assessed with the Peds-QL gastrointestinal scales (Peds-QL GIS)[24] as a comparator.

Participants

Age Range. Participants aged 13-18 years were included. The choice to set the lower age limit at 13 years was dictated partly by the recommended age of the comparators used for convergent validity analysis. Most comparators were validated for adolescents older than 13 years; therefore, they may not have accurately captured data of younger adolescents. The Spider questions also require sufficient cognitive abilities to understand the questions asked but also their symptoms and the effect these have on daily life.

Diagnosis. Adolescents were invited to participate if they met the inclusion criteria (**Table I**). The researchers recognize the diagnostic challenges for children and young people whose clinical profiles are still developing and who may not have received formal diagnoses of HSD/hEDS. Participants with diagnoses of HSD, hEDS, or SH were accepted to allow inclusion of those with comorbid symptoms but without formal diagnosis of HSD/hEDS. From this point forward, these participants will be grouped and referred to as "SH group."

Table I. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Aged between 13 and 18 y (stages 1, 3, and 4)	Younger than 13 or older than 18 y (stages 1, 3, and 4)
Aged between 12 and 18 y (stage 2)	Younger than 12 and older than 18 y (stage 2);
	Unrelated neurologic comorbidities (eg, cerebral palsy)
Diagnosis of HSD/hEDS/SH	Unrelated musculoskeletal comorbidities (eg, a traumatic injury)
No SH (known group)	Unrelated rheumatological comorbidities (eg, juvenile idiopathic arthritis)
Able to understand and communicate in English	GHJ with no symptoms

GJH, generalized joint hypermobility.

Recruitment. Three hypermobility charities (Hypermobility Syndromes Association, Ehlers Danlos Support UK, and the Ehlers Danlos Society) and a private hypermobility unit (Central Health London Hypermobility Unit) aided recruitment through advertisement on their websites, social media pages, or via email. Participant recruitment used self-selection and snowball sampling methods. An information sheet outlining the study's purpose and methods was provided with the questionnaire link and participants were encouraged to share the studies with both friends or relatives with and without hypermobility.

Procedure

Adolescents who agreed to participate accessed the survey via REDCap, an online survey hosting platform. Participants, and parents of those younger than 18 years, read an information sheet and consented before proceeding. Participants provided demographic information (including age, sex assigned at birth, ethnicity, location, diagnosis, and the clinician who provided the diagnosis) and answered the Spider domain and comparator questions. All data were collected anonymously.

Data Management and Analysis

Data were processed using IBM SPSS, version 27 (IBM Corp) for descriptive and inferential statistics. Incomplete data or data from participants outside of age limits were excluded from analysis. Participants were categorized into SH groups and control groups (no hypermobility). Normality was assessed through visual histogram inspection and Shapiro-Wilk calculations. Differences between the SH and control group were analyzed using the χ^2 test or Fisher exact test for categoric data and independent *t*-tests or Mann-Whitney *U* tests for numeric data (depending on assessment of normality). Convergent validity was assessed in the SH group by examining correlations between the scores of the Spider domains and their respective comparator questionnaire. Nonparametric Spearman rho analysis was used, as this better captures the monotonic relationships between variables. Correlations below $r < 0.50$ were considered unacceptable, $r > 0.6$ considered moderate to high, and $r > 0.7$ considered strong.[25] Known-group validity was determined by comparing average scores of the Spider domains from the SH and control groups using a Mann-Whitney *U* test after assessing normality. A significance level of $P < .05$ was considered statistically significant and 95% CIs were calculated using SPSS bootstrapping.

Role of the Funding Source

Funding supported staff salaries, conference attendance, and open journal access costs. The funders were not involved in determining study design, data analysis, or the decision to submit the article for publication.

Results

Participants

Overall, 1154 adolescents were included from an initial cohort of 2131 (Figure 2). There were 1036 participants with SH and 118 controls. Demographic data are presented in Table II. Stage 1 recruited 232 participants with SH and 40 controls aged 13-18 years. There were no significant between-group differences. Stage 2 initially recruited 233 participants aged 12-18 years. Twelve-year-old participants were recruited in this study because of the suggested age range of the RCADS-25; however, data from 12-year-old participants were excluded post-hoc, as all other Spider domains were validated with 13- to 18-year-old participants. Data from 217 participants were therefore analyzed, 196 in the SH group and 21 controls. There was a significant between-group difference in sex ($P = .037$) and ethnicity ($P = .041$). Stage 3 recruited 305 participants with SH and 27 controls aged 13-18 years. There were no between-group differences. Stage 4 recruited 303 participants with SH and 30 controls aged 13-18 years. There were no between group differences.

Construct Validity

Construct validity assessment included establishing each domain's convergent validity (Table III) and known-group validity (Figure 3).

Convergent Validity. For stage 1, a strong positive correlation was found between the Spider pain domain and the CALI-9 ($r = 0.70$), and a strong negative correlation was found between the Spider fatigue domain and the MFS ($r = -0.70$). The negative correlation was expected as the result of opposite scoring methods of MFS (greater scores mean less affected). For stage 2, the Spider depression domain and the RCADS-25 depression domain were strongly correlated ($r = 0.79$), and the Spider anxiety domain and the RCADS-25 anxiety domain ($r = 0.60$) showed a moderate correlation. For stage 3, strong correlations were found between the Spider cardiac domain and the COMPASS-31 ($r = 0.74$) and the Spider neuromusculoskeletal domain and the BIoH ($r = 0{\cdot}72$). A moderate correlation was shown between the Spider urogenital domain and DVSS ($r = 0.61$). For stage 4, strong negative correlations were found between

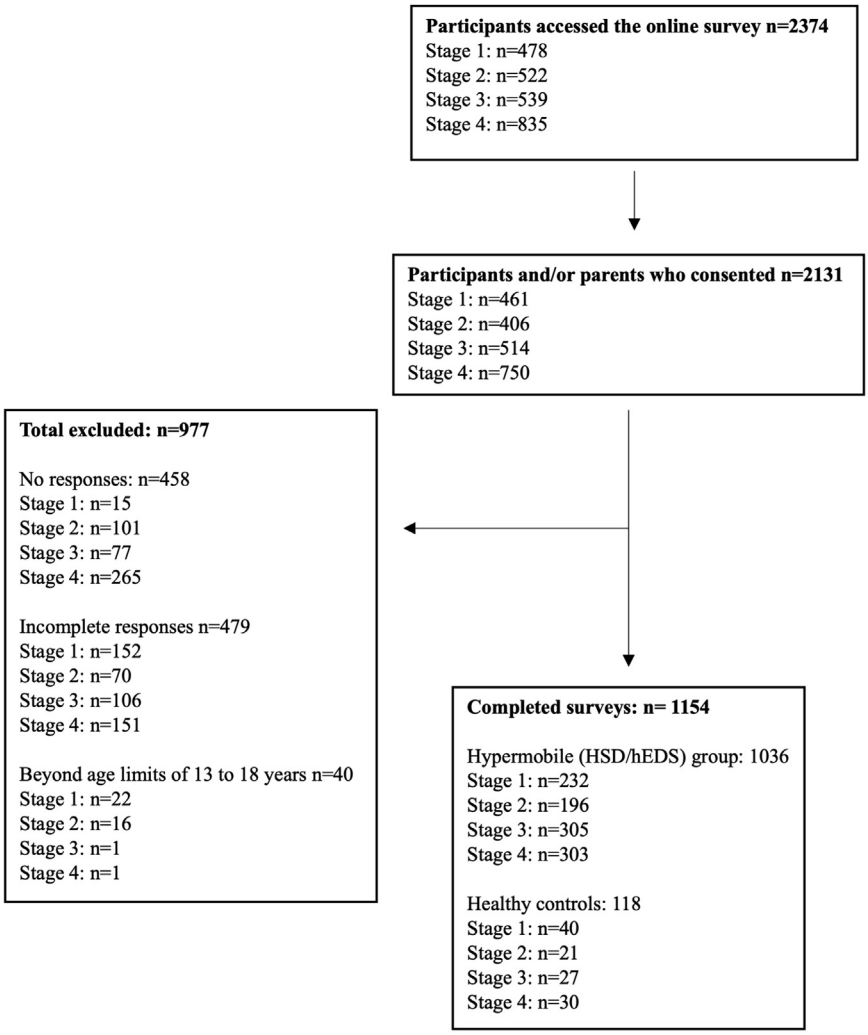

Figure 2. Participant recruitment flow diagram.

the Spider gastrointestinal domain and the Peds-QL GIS (r = −0.80). The negative correlation was expected as the result of reverse scoring methods of Peds-QL GIS, with greater scores meaning less affected.

Known-Group Validity. For stage 1, there was a significant difference ($P < .001$) in Spider scores between those with and without SH in both the pain (43.8 [31.3-62.5] and 6.3 [6.3-18.8]) and fatigue domains (58.3 [41.7-75] and 16.7 [8.3-41.7]) respectively. For stage 2, there was a significant difference ($P < .001$) in Spider scores between those with and without SH in both the anxiety (50 [33.3-58.3] and 8.3 [0-25]) and depression domains (41.7 [25-58.3] and 0 [0-16.7]) respectively. For stage 3, there was a significant difference ($P < .001$) in Spider scores between the SH and control groups in the cardiac dysautonomia (57.5 [33.8-76.3] and 16.3 [5-41.3] and neuromusculoskeletal domains (50 [31.3-68.8] and 18.8 [0-37.5]). The urogenital domain did not show a significant difference between the SH and control groups scores (15 [2.5-30] and 6.7 [0-20] respectively), likely the result of reduced numbers of participants reporting bladder symptoms ($P = .094$). For stage 4: the Spider gastrointestinal domain demonstrated the ability to differentiate between the hypermobile and the control group Spider scores (37.5 [25-56.3] and 12.5 [6.3-31.3] respectively $P < .001$).

Discussion

This study is the first of its kind, to our knowledge, presenting the Spider, a unique, hypermobility-specific questionnaire that quickly and easily determines an adolescent's multisystemic symptom profile. This study aimed to evaluate construct validity of the Spider in a large group of adolescents. The Spider questionnaire demonstrates acceptable convergent validity. All domains showed moderate or strong correlations with the most appropriate comparator questionnaire. Known-group validity was established in 7 of the 8 domains, suggesting those Spider

Table II. Demographic characteristics of participants in all stages

	Stage 1			Stage 2			Stage 3			Stage 4		
Demographic characteristics	**SH n = 232**	**Controls n = 40**	**Significance *P* value**	**SH n = 196**	**Controls n = 21**	**Significance *P* value**	**SH n = 305**	**Controls n = 27**	**Significance *P* value**	**SH n = 303**	**Controls n = 30**	**Significance *P* value**
Age, y*	16.1 ± 1.7	16.2 ± 1.6	.74	16 (3)	15 (4)	.130	16 (3)	16 (3)	.540	17 (3)	16 (4)	.086
Sex†												
Female	189 (81.5%)	28 (70%)	.1	162 (82.7%)	13 (61.9%)	.037‡	259 (84.9%)	23 (85.2%)	.970	241 (79.5%)	19 (63.3%)	.092
Intersex	0	0		0	0		0	0		5 (1.7%)	0	
Male	43 (18.5%)	12 (30%)		34 (17.3%)	8 (38.1%)		46 (15.1%)	4 (14.8%)		57 (18.8%)	11 (36.7%)	
Ethnicity†												
Asian/Asian British	3 (1.3%)	3 (7.5%)	.13	3 (1.5%)	2 (9.5%)	.041‡	5 (1.6%)	0	.879	2 (0.7%)	0	.886
Black/African/ Caribbean/Black British	3 (1.3%)	1 (2.5%)		0	0		1 (0.3%)	0		3 (1%)	0	
Mixed/multiple ethnicity	7 (3%)	2 (5%)		11 (5.6%)	3 (14.3%)		9 (3%)	1 (3.7%)		14 (4.6%)	1 (3.3%)	
Others	1 (0.4%)	0		5 (2.6%)	0		8 (2.6%)	0		6 (2%)	1 (3.3%)	
White	218 (94%)	34 (85%)		177 (90.3%)	16 (76.2%)		282 (92.5%)	26 (96.3%)		278 (91.7%)	28 (93.3%)	
Country of residence†												
Asia	0	2 (5%)	.1	1 (0.5%)	0	.148	2 (0.7%)	0	.121	0	0	.393
Australia/Oceania	15 (6.5%)	0		7 (3.6%)	1 (4.8%)		12 (3.9%)	0		23 (7.5%)	2 (6.7%)	
Europe	8 (3.4%)	0		10 (5.1%)	0		16 (5.2%)	1 (3.7%)		13 (4.3%)	0	
North America and Canada	50 (21.6%)	0		50 (25.5%)	1 (4.8%)		101 (33.1%)	3 (11.1%)		113 (37.4%)	7 (23.3%)	
Republic of Ireland	20 (8.6%)	0		5 (2.6%)	0		7 (2.3%)	0		4 (1.3%)	0	
South America	0	0		0	0		2 (0.7%)	0		2 (0.7%)	0	
United Kingdom	139 (59.9%)	38 (95%)		123 (62.8%)	19 (90.5%)		165 (54.1%)	23 (85.2%)		149 (48.9%)	21 (70%)	

SH, symptomatic hypermobility group.
*Numeric data displayed as mean ± SD or median (IQR).
†All other categorical data displayed as counts and frequencies in percentages (%).
‡Significance level $P < .05$.

Table III. Convergent validity of each Spider domain

The spider domains	Correlated with PROMs	Spearman correlation (r)	95% CI*	*P* value
Fatigue	MFS	−0.70	−0.77 to −0.62	<.0001†
Pain	Child Activity Limitations Interview-9	0.70	0.61-0.78	<.0001†
Anxiety	RCADS-25	0.60	0.51-0.68	<.0001†
Depression	RCADS-25	0.79	0.72-0.84	<.0001†
Urogenital	DVSS	0.61	0.53-0.68	<.0001†
Cardiac dysautonomia	COMPASS-31	0.74	0.67-0.79	<.0001†
Neuromusculoskeletal	BloH	0.72	0.65-0.78	<.0001†
Gastrointestinal	Peds-QL GIS	−0.80	−0.75 to −0.84	<.0001†

*CIs presented as lower limit to upper limit and calculated through bootstrapping in SPSS. Correlations over r = 0.5 are acceptable, r = 0.6 moderate, and r = 0.7 strong.
†Significance level $P < .05$.

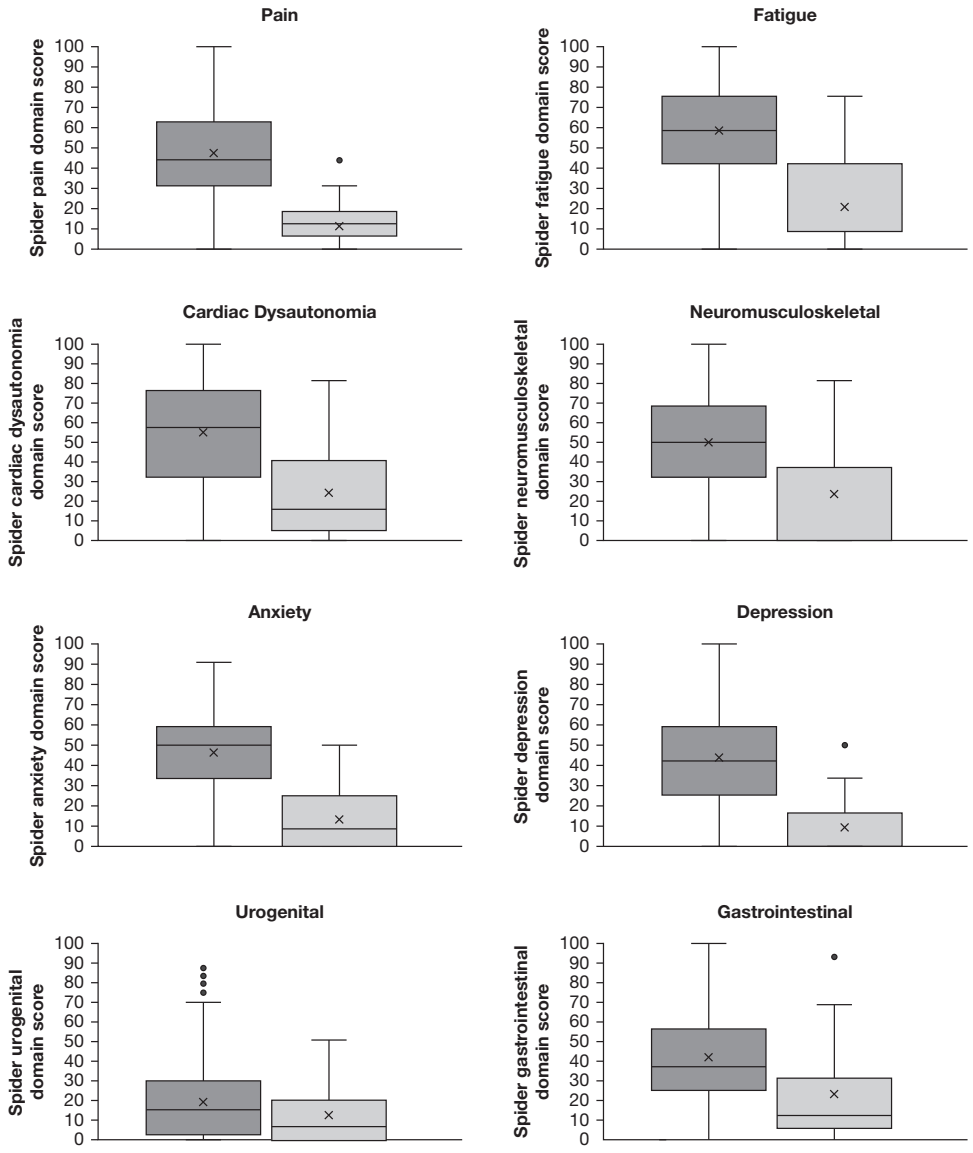

Figure 3. Box and whisker plots showing known group validity. *Dark gray* and *light gray boxes* represent the hypermobile group and control group, respectively. Average score presented as mean ± SD or median (IQR). Range of scores (excluding outliers) represented by *upper and lower whisker lines*, quartiles represented by the *box*, mean or median represented by the *middle quartile line*, and outliers shown by single data points. *Significance level $P < .05$.

domains can distinguish between individuals with and without SH. This tool quickly and concisely assesses musculoskeletal symptoms, and the often-overlooked nonmusculoskeletal symptoms, without the need for multiple PROMs, taking most less than 10 minutes to complete. It is likely to increase awareness of the multisystemic nature of HSD/hEDS. It may be used by any clinician involved in the care of an adolescent with HSD/hEDS to guide conversation, highlight areas of greatest need, prioritize symptom management, and encourage a multidisciplinary management approach. The Spider's visual representation of symptoms can easily identify concerns, guide onward referral, and encourage individualized management. The Spider is also accessible to patients, who may complete it independently and use the results to guide discussions regarding their care needs.

The Spider assesses the presence and impact of 8 key commonly associated symptom domains. Comparator PROMs were selected basis of their applicability, psychometric qualities, and recommendations from the Ehlers Danlos Society Internal Consortium Common Data Element work.[26] Given the diverse yet specific nature of hypermobility comorbid symptoms/conditions and the limited availability of questionnaires specifically developed for this purpose, the researcher team recognized the lack of gold standard or extensively validated comparators in the target population for some symptom domains. This is echoed by COSMIN, who acknowledge a lack of a gold standard against which to examine the construct validity of a PROM.[16] There were limited comparators assessing urogenital, neuromusculoskeletal, and cardiac dysautonomia symptoms with adolescents. For the urogenital domain, the DVSS was chosen over the commonly used Pediatric Icontinence Questionnaire (PinQ) as the result of incompatible concepts. The PinQ primarily measures the effect of urogenital symptoms on quality of life, whereas the Spider assesses the presence of symptoms and their effect on daily function. The effect these symptoms have on quality of life cannot be inferred from Spider results, making the PinQ a less-suitable comparator. Because of the specific nature of neuromusculoskeletal and cardiac symptoms in people with HSD/hEDS, limited comparator options were available. Expert clinician opinions led to the use of specific questions from the BIoH and COMPASS-31 because of their conceptual similarity to the corresponding Spider domains.

All Spider domains demonstrated acceptable convergent validity, adequately correlating to the concept of the selected comparator questionnaire, with 95% CIs remaining above the recommended correlation of $r > 0.5$.[25] However, the presence and effect of urogenital symptoms in this sample was low to moderate, with average scores of 10 of 30 on the DVSS and 15 of 100 on the Spider. This skewness resulted in an inability to assess validity across the full scale, potentially affecting both convergent and known-group validity of this domain. This may also suggest that urogenital symptoms were less impactful in this sample of adolescents and may be more prevalent in childhood and/or adulthood, highlighting a future research question.

Strengths and Limitations

During the development of the Spider, patient and public involvement were paramount to ensure the questions asked were relevant and important. Both clinical experts and members of the public were consulted during development, particularly when deciding item content, wording, and reduction. This collaboration increased the Spider's ability to reflect the concerns most important to those treating and living with HSD/hEDS. Despite each Spider domain having between 3 and 5 questions, compared with up to 58 questions in comparator questionnaires, the Spider converged well with comparators while retaining brevity. It offers an assessment of multisystemic comorbid symptoms/conditions in less than 10 minutes, avoiding the time-consuming burden of completing 8 separate questionnaires. It can be used in clinical settings without compromising appointment time or patient energy.

Because participants were recruited via international charities, the sample sizes of each stage were large and multinational. Across all studies, there was a larger proportion of older, female adolescents. Evidence suggests JH increases in female adolescents after puberty begins[27] between 8.8 and 13.2 years of age[28] and may explain the greater proportion of female participants in the SH group. Although this is generally representative of the hypermobile population, the disparity is larger than anticipated.[29] The sample was predominantly White, with limited representation from other ethnic backgrounds despite international reach. Self-selection recruitment techniques may have introduced bias, resulting in under-representation of diverse ethnicities and males and limiting generalizability of results to these groups. Snowball sampling, although extending the study's reach, may have increased sample homogeneity, as referrals may have been between groups with similar characteristics.[30] Participants self-selected and self-reported their diagnosis, which could not be corroborated with a physical examination.

Developments and Further Research

A digital application is being developed for worldwide, cost-free use by clinicians and researchers. In research, the Spider can be used to track the natural history of HSD/hEDS and its comorbid symptoms over time. This could allow investigation of the influence of demographic characteristics on the presence and impact of symptoms, and identification of determinates for more severe prognosis. The Spider scores may help identify patient subgroups with similar symptom profiles and help describe differences among various heritable connective tissue disorders. Ongoing research aims to assess further psychometric properties of the Spider, including construct validity of the Spider's total score, construct validity with adults, and internal consistency, test-retest reliability, and factor structure analysis with adolescents and adults. Further research also should include the use of survey promotion tools targeted at a more diverse population to ensure data are more widely representative. The research team plans to establish minimal clinically important differences and to translate the Spider to increase

international accessibility. This innovative approach to assessing the multisystemic symptoms associated with HSD/hEDS has the potential to extend to other heritable connective tissue disorders in the future.

Conclusions

This study series investigated the construct validity of the Spider domains in the adolescent HSD/hEDS population, demonstrating statistically significant convergent validity in all domains and statistically significant known-group validity in 7 domains. The Spider provides clinicians and researchers with a novel, freely accessible, efficient, and valid tool for assessing multisystemic symptom profiles of adolescents with HSD/hEDS. This will enable individualized, holistic patient care tailored to meet the specific needs of young people with HSD/hEDS. ■

CRediT authorship contribution statement

Ellen Ewer: Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft. **Hanadi Kazkaz:** Conceptualization, Investigation, Resources, Writing – review & editing. **Nelly Ninis:** Conceptualization, Resources, Writing – review & editing. **Peter Rowe:** Conceptualization, Resources, Writing – review & editing. **Robby De Pauw:** Data curation, Formal analysis, Methodology, Software, Writing – review & editing. **Eudora Tang:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Cathy Barrett:** Methodology, Writing – review & editing. **Lies Rombaut:** Resources, Writing – review & editing. **Inge De Wandele:** Conceptualization, Funding acquisition, Methodology, Resources, Supervision, Writing – review & editing. **Jane V. Simmonds:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Declaration of Competing Interest

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Data Statement

Data sharing statement available at www.jpeds.com.

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