REVIEW ARTICLE

Hypermobile Ehlers–Danlos syndrome and disorders of the gastrointestinal tract: What the gastroenterologist needs to know

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Abstract

Background and Aim: Hypermobile Ehlers–Danlos syndrome (hEDS) and the hypermobility spectrum disorders (HSD) can be challenging to diagnose and manage. Gastrointestinal symptoms and disorders of gut-brain interaction are common in this cohort and multifactorial in origin. The primary aim of this review is to arm the gastroenterologist with a clinically useful understanding of HSD/hEDS, by exploring the association of gastrointestinal disorders with HSD/hEDS, highlighting current pathophysiological understanding and providing a pragmatic approach to managing these patients.

Methods: Literature relevant to the gastrointestinal system and hypermobile Ehlers–Danlos syndrome was systematically searched, critically appraised, and summarized.

Results: Diagnosis is based upon clinical criteria and a genetic basis is yet to be defined. The prevalence of many gut symptoms, including abdominal pain (69% vs 27%, $P < 0.0001$), postprandial fullness (34% vs 16%, $P = 0.01$), constipation (73% vs 16%, $P < 0.001$), and diarrhea (47% vs 9%, $P < 0.001$) are significantly higher in HSD/hEDS compared with non-HSD/hEDS individuals. Disorders of gut-brain interaction are also common, particularly functional dyspepsia. The pathophysiology of gut symptoms is poorly understood but may involve effects of connective tissue laxity and its functional consequences, and the influence of autonomic dysfunction, medication and comorbid mental health disorders. Awareness is the key to early diagnosis. Management is limited in evidence-base but ideally should include an integrated multidisciplinary approach.

Conclusions: HSD/hEDS is a multisystemic disorder in which gastrointestinal symptoms, particularly related to disorders of gut-brain interaction are common. Deficiencies in knowledge regarding the pathophysiological processes limit evidence-based interventions and remain important areas for future research.

Introduction

Ehlers–Danlos syndrome (EDS) was first recognized in the time of Hippocrates in the fourth century BC. Appreciation of its heterogeneity continues to evolve to this day. EDS is the most common non-inflammatory connective tissue disorder featuring joint hypermobility, with the hypermobile EDS (hEDS) subtype representing 80–90% of the burden of disease.[1,2] hEDS is now recognized as part of the "hypermobility spectrum disorders" (HSD), which are characterized by varying articular and extra-articular involvement and impact on quality of life. The vast majority of those affected are female, gastrointestinal symptoms are very common and healthcare utilization is high.[3–5] Many patients meet diagnostic criteria for disorders of gut-brain interaction (DGBI), but the pathophysiological link between DGBI and HSD/hEDS is yet to be established beyond association. The primary aim of this review is to arm the gastroenterologist with a clinically useful understanding of HSD/hEDS, by exploring the association of gastrointestinal disorders with HSD/hEDS, highlighting current pathophysiological understanding and providing a pragmatic approach to managing these patients.

Methodology

In order to perform this narrative review, the published literature was systematically searched via PubMed, ProQuest and OVID using key words that included hypermobile Ehlers–Danlos syndrome, hEDS, joint hypermobility syndrome, gastrointestinal disorders, functional gut disorders, disorders gut-brain interaction, functional dyspepsia, irritable bowel syndrome, constipation, diarrhea, rectal evacuatory dysfunction, autonomic function, and motility. Each subsection was additionally explored using targeted searching, for example, "eating disorder" and hypermobile Ehlers–Danlos Syndrome. Abstracts were appraised and relevant articles were then reviewed and analyzed in full. Additional studies were located via cross-referencing. Studies in pediatric cohorts were not included.

Terminology and diagnostic criteria

A major hindrance to the general understanding of EDS has been its heterogeneity, in part related to the multiple classification systems used over the years. The current nosology and diagnostic criteria are defined by the 2017 International Classification of the Ehlers–Danlos Syndromes in which 13 variants are recognized (Table S1) although an additional subtype was added provisionally in 2018 and is referred to as classical-like type 2 EDS.[6,7] Recognized genetic mutations simplify the diagnosis for nearly all subtypes. The exception is hEDS, where the genetic basis has not been established.[8] As a result, the diagnosis of hEDS relies on clinical features (Table 1). Central to the diagnosis of hEDS is the Beighton score, which evaluates joint hypermobility using established criteria (Fig. 1, Table 1).[9]

Table 1 New diagnostic criteria for hypermobile Ehlers–Danlos syndrome (hEDS)[7]

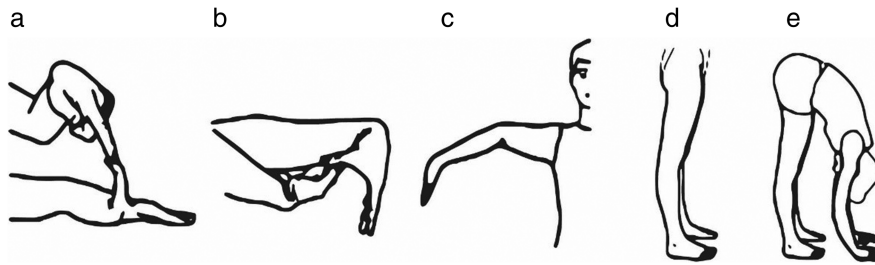|		
Criterion 1: *Must be met*	The Beighton score for generalized joint hypermobility	• Prepubertal children/adolescents: > 6 • Men, women post puberty to age 50: > 5 • Over age 50: > 4 • *If one point below diagnostic, score* ≥ 2 *in the 5-point questionnaire indicates the presence of joint hypermobility (sensitivity 80–85%, specificity 80–90%)*[10]
Criterion 2: *Two or more of the following features*	**Feature A:** Systemic manifestations of a more generalized connective tissue disorder	At least five of the following must be present: • Unusually soft or velvety skin • Mild skin hyperextensibility (skin stretch > 1.5 cm distal forearm/dorsum hand; > 3 cm neck/elbow/knee; > 1 cm palmar surface hand) • Unexplained striae (without a history of significant weight change) • Bilateral piezogenic papules of heel (small, tender herniations of adipose globules through fascia into dermis) • Recurrent or multiple abdominal hernias • Atrophic scarring involving at least two sites • Pelvic floor, rectal and/or uterine prolapse in children, men or nulliparous women without a history of morbid obesity or predisposing medical condition • Dental crowding and high or narrow palate • Arachnodactyly • Arm span-to-height ratio ≥ 1.05 • Mitral valve prolapse (based on strict echocardiographic criteria) • Aortic root dilatation with *z*-score > +2 (i.e. > 2 SD above the size and gender specific population mean) • ≥ 1 first-degree relative with hEDS
	Feature B: Positive family history	
	Feature C: Musculoskeletal Complications	One of the following: • Musculoskeletal pain in ≥ 2 or more limbs, recurring daily for at least 3 months • Chronic, widespread pain for ≥ 3 months • Recurrent joint dislocations or frank joint instability, in the absence of trauma
Criterion 3: *All must be met*		• Absence of unusual skin fragility that should prompt consideration of other types of EDS • Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions • In patients with an acquired/autoimmune connective tissue disorder, must meet both Features A and B of Criterion 2. Feature C of Criterion 2 (chronic pain and/or instability) cannot be counted • Exclusion of alternative diagnoses that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity

Figure 1 Beighton scoring system measures joint hypermobility on a 9-point scale. Joints assessed (left to right) include (a) passive dorsiflexion of fifth finger $\geq 90°$ (one point per side); (b) passive apposition of the thumb to ipsilateral forearm (one point per side); (c) hyperextension of the elbow $\geq 10°$ (one point per side); (d) hyperextension of the knee $\geq 10°$ (one point per side); and (e) spinal assessment (one point if both palms reach the floor when bending over with knees locked in extension and feet together). Redrawn from Malfait *et al.* (2017) with permission.

Various terms have been used historically to describe this group of hypermobile patients, the most common being "joint hypermobility syndrome" (JHS), which includes patients who meet the current hEDS criteria, but also some who do not. To declutter the confusing nomenclature, the term "hypermobility spectrum disorder" (HSD) is now used as an umbrella term (Fig. 2). hEDS is considered to sit on the more severe end of the spectrum as it is associated with significant somatic complaints related to musculoskeletal manifestations such fibromyalgia (40%), chronic fatigue (38%), and pain (almost 100%) (acute and chronic, nociceptive, neuropathic, and nociplastic).[2,5,11–13] In addition, various non-musculoskeletal manifestations can be present including, neurological (e.g. headaches), psychiatric and neurodevelopmental (e.g. mood disorders, anxiety, and sleep disturbances), cardiorespiratory (e.g. palpitations, chest pain, and dyspnea), autonomic (e.g. syncope, postural instability, and thermoregulatory difficulties), urogynecological (e.g. prolapse, urinary incontinence, and dyspareunia), and gastroenterological.[2,5,12,14–18] Inflammatory and systemic manifestations, postulated to relate to mast cell activation, are also reported.[19] Given the complexity of the historical nomenclature and in order to incorporate published data that have utilized previous terminology, the disorder will be referred to as "HSD/hEDS" (unless specifically describing hEDS) for this review. It is acknowledged that this will introduce some phenotypic and genotypic heterogeneity. Using this definition, it is estimated that the prevalence of HSD/hEDS is greater than 1:500.[20]

Hypermobility spectrum disorders/hypermobile Ehlers-Danlos syndrome and the gastrointestinal system

The association between gastrointestinal symptoms and HSD/hEDS was first described 15 years ago.[15] A vast array of
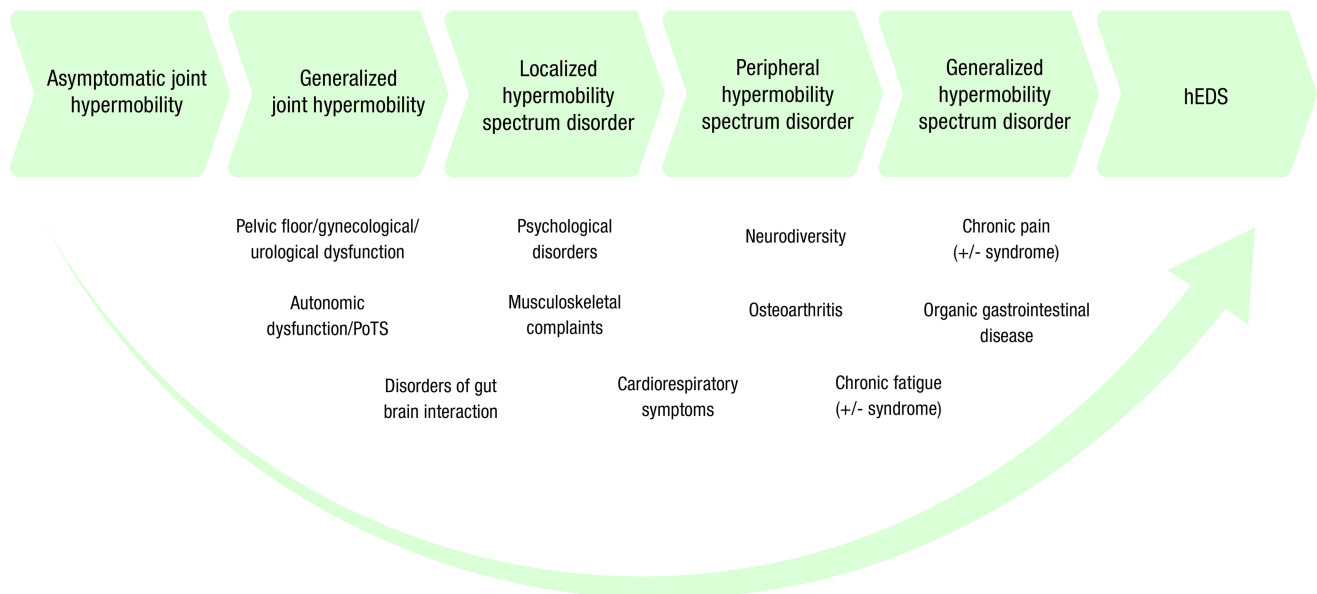
Figure 2 Spectrum of joint hypermobility. The horizontal arrows depict the spectrum of joint disease, ranging from asymptomatic, non-syndromic joint hypermobility, progressing through the newly recognized hypermobility spectrum disorder with various combinations of musculoskeletal and non-musculoskeletal manifestations (insufficient to meet the criteria for hEDS). Also depicted are the common manifestations contributing to the somatic complaints described. PoTS, postural orthostatic tachycardia syndrome.

symptoms occur significantly more often in HSD/hEDS compared with non-HSD/hEDS patients (Fig. 3). Commonly, more than one gastrointestinal symptom is present.[5,21,22] A greater severity and extent of gastrointestinal involvement has been described in patients referred to gastroenterology clinics with a pre-existing diagnosis of HSD/hEDS, compared with patients with features of HSD/hEDS but without a prior diagnosis, followed by those without any features of HSD/hEDS.[4]

Despite many studies, the true prevalence of gastrointestinal disorders in this cohort is difficult to assess due to varying nomenclature and methodological biases, particularly selection bias, in the studies published. Moreover, the reported prevalence of gastrointestinal symptoms varies widely depending on whether it is derived from population-based studies, support groups, non-gastroenterological specialist (genetics, cardiology and rheumatology) clinics (Table 2) and gastroenterology clinics (Table 3).[4,14,23–28] Nevertheless, gastrointestinal symptoms have been associated with impairment of quality of life in patients with HSD/hEDS in each of the study settings.[3–5,22,27]

Association with disorders of gut-brain interaction. Criteria for DGBI are met frequently in patients with HSD/hEDS, in both the community and hospital settings. For example, 94% in HSD/hEDS survey respondents from the UK EDS support group fulfilled criteria for DGBI compared with 47% of the control population ($P < 0.0001$) and 91% in rheumatology-referred HSD/hEDS patients compared with 48% of non-HSD/hEDS patient referrals.[4,5] Moreover, patients seeking gastroenterological review for DGBI were more likely to meet diagnostic criteria for HSD/hEDS than those presenting with organic disorders (39% *vs* 28%, $P = 0.002$).[22]

Dyspeptic symptoms are common and the diagnosis of functional dyspepsia by both Rome III and IV criteria appears to be more common in HSD/hEDS compared with controls in both gastroenterology (OR 2.08, CI 1.25–3.46 for functional gastroduodenal disorders, $P = 0.005$), and non-gastroenterology hospital clinics (38% *vs* 9%, $P = 0.029$), support groups (57% *vs* 9%, $P < 0.0001$) and the general population (39% *vs* 23%, $P = 0.02$).[5,21,22,27] There appears to be no difference in the type or patterns of symptoms in patients with functional dyspepsia with or without HSD/hEDS.[29]

The prevalence of other DGBI in the HSD/hEDS population have been inconsistently assessed (Tables 2 and 3). Irritable bowel syndrome (IBS) has a similar prevalence in HSD/hEDS patients referred to gastroenterology clinics (OR 1.34, CI 0.90–2.00, $P = 0.15$)[22] and in the general population examined for gut symptoms and hypermobility,[21] although studies conducted through support groups and non-gastroenterology clinics have found IBS to be generally more common than in the non-HSD/hEDS
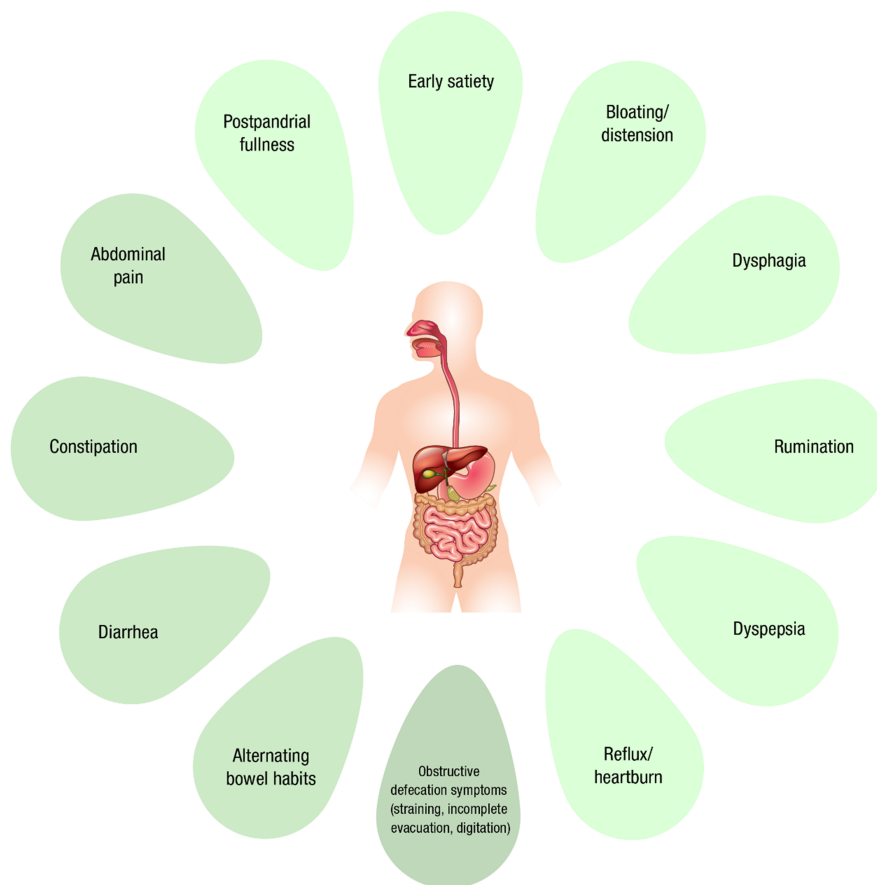

Figure 3 Various gastrointestinal symptoms have been reported to occur significantly more often in patients with HSD/hEDS compared with non-HSD/hEDS controls. See Tables 2 and 3.

Table 2 Overview of gastrointestinal symptoms observed in studies of patients with hypermobilility spectrum disorder/hypermobile Ehlers–Danlos Syndrome (HSD/hEDS) (excluding studies in gastroenterology specialist clinics)

Author, year	Classification utilized	Study type	Study setting and number of patients	Symptom prevalence
Castori *et al.*, 2010[3]	Villefranche criteria + Brighton criteria	Observational cross-sectional	General genetics outpatients; Italy *n* = 21 (18 female)	Reflux/heartburn (57%); dyspepsia (67%); abdominal pain (62%); constipation/diarrhea (33%); hernias (abdominal) (5%)
Castori *et al.*, 2011[25]	Villefranche criteria + Brighton criteria	Observational cross-sectional	Multidisciplinary joint hypermobility clinic; Italy Cumulative prevalence of symptoms according to age reported—based on patient recall *n* = 50 (44 female)	By age ≥ 40 years: reflux/heartburn (74%); abdominal pain (68%); chronic gastritis (48%); alternating bowel habits (72%); hernias (abdominal) (20%)
Mastoroudes *et al.*, 2013[31]	Revised 1998 Brighton criteria	Observational case–control	Hypermobility clinic; UK *n* = 60 HSD/hEDS; 60 age-matched and sex-matched controls from medical staff	Obstructive defecation symptoms: 23% *vs* 5% controls (P = 0.007); straining: 62% (P < 0.001); incomplete evacuation: 63% (P < 0.001); digitation: 33% (P = 0.001); constipation: 72% (P < 0.001)
Zeitoun *et al.*, 2013[28]	Villefranche criteria	Observational cross-sectional	EDS patient support group; France *n* = 134 (122 female); 108 HSD/hEDS 64% survey response rate	Nausea (71%); reflux/heartburn (69%); dysphagia (63%); regurgitation (69%); postprandial fullness (67%); belching (71%); epigastric pain (71%); constipation (36%); IBS-like symptoms (48%)
Castori *et al.*, 2014[24]	Villefranche criteria	Observational cross-sectional	Pedigrees were selected from two Italian outpatient clinics for EDS and inherited connective tissue disorders. 23 families with HSD/hEDS (*n* = 82)	Reflux/heartburn (34%); chronic gastritis (23%); abdominal pain (20%); constipation (28%)
Nelson *et al.*, 2015[14]	Villefranche criteria + Brighton criteria	Observational retrospective	Medical Genetics Clinic (1994–2013) 687 EDS patients (*n* = 471 HSD/hEDS) No control group included	HSD/hEDS *vs* other EDS: constipation: 42% *vs* 29% (P = 0.02); nausea: 44% *vs* 37%; reflux/heartburn: 38% *vs* 36%; vomiting: 25% *vs* 22%; waterbrash: 1% *vs* 2%; dysphagia: 11% *vs* 12%; regurgitation: 4% *vs* 6%; postprandial fullness: 7% *vs* 3%; bloating: 17% *vs* 10%; dyspepsia: 11% *vs* 7%; abdominal pain: 56% *vs* 56%; diarrhea: 23% *vs* 17%; fecal urgency: 1.5% *vs* 2.8%
Fikree *et al.*, 2017[21]	Villefranche criteria + Brighton criteria	Cross-sectional, double-blinded, case–control	University students (without prior diagnosis of HSD/hEDS); UK HSD/hEDS: *n* = 74 (48 female) Controls: *n* = 88	HSD/hEDS *vs* controls: postprandial fullness: 34% *vs* 16% (P = 0.01); early satiety: 32% *vs* 17% (P = 0.03); bloating: 26% *vs* 23% (P = 0.59); functional dyspepsia: 39% *vs* 23% controls (P = 0.02); No differences in lower gastrointestinal symptoms (IBS, constipation, diarrhea, alternating bowel habit, ≤ 4 bowel motions/week).
Inayet *et al.*, 2018[27]	Not specified	Observational cross-sectional, case–control	Cardiology and rheumatology clinics; UK 45 Marfan syndrome and 45 HSD/hEDS (33 female) 90 age-matched and sex-matched controls	HSD/hEDS *vs* controls: functional abdominal pain: 69% *vs* 27% (P < 0.001); functional constipation: 73% *vs* 16% (P < 0.001); functional diarrhea: 47% *vs* 9% (P < 0.001); IBS: 33% *vs* 7% (P = 0.0014); functional heartburn: 47% *vs* 13% (P = 0.0011);

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Table 2 (Continued)

Author, year	Classification utilized	Study type	Study setting and number of patients	Symptom prevalence
				functional dyspepsia: 38% *vs* 9% control (*P* = 0.029); functional bloating/distension: 31% *vs* 7% (*P* = 0.006)
Nee *et al.*, 2019[23]	Not specified (Villefranche and Berlin nomenclature accepted)	Observational, cross-sectional	Members of local and national Marfan and EDS societies; US EDS: *n* = 1804 HSD/hEDS, *n* = 1325); MFS: *n* = 600); 94% female	HSD/hEDS *vs* other subtypes of EDS: aerophagia: 24% *vs* 26% (*P* = 0.35); bloating: 13% 12%; heartburn: 32% *vs* 37% (*P* = 0.04); dysphagia: 29% *vs* 28%; IBS: 58% *vs* 56%; functional constipation: 8% *vs* 7%; diarrhea: 0.5% *vs* 1.3%; functional dyspepsia: 55% *vs* 56%
Alomari *et al.*, 2020[36]	2017 International classification of EDS	Observational retrospective	Genetics clinic; US *n* = 218 (198 female)	63% gastrointestinal symptoms at hEDS diagnosis (63%); abdominal pain (50%); nausea (50%); constipation (45%); diarrhea (38%); heartburn (36%); belching/bloating (27%); vomiting (26%); IBS-like symptoms (22%); dysphagia (14%); fecal incontinence (6%)
Lam *et al.*, 2020[5]	Not specified	Case–control	EDS support group; UK HSD/hEDS: *n* = 603 Age-matched and sex-matched controls: *n* = 1994 Mean age: 39 years, 96% female 20% survey response rate	HSD/hEDS *vs* control: functional dyspepsia: 57% *vs* 9% (*P* < 0.0001); IBS: 54% *vs* 8% (*P* < 0.001); functional dysphagia: 42% *vs* 4% (*P* < 0.001); rumination: 31% *vs* 5% (*P* < 0.001); functional constipation: 12% *vs* 10%; functional diarrhea: 5% *vs* 4.6%; functional anorectal disorders: 53% *vs* 9% (*P* < 0.001)
Tai *et al.*, 2020[71]	Not specified	Observational cross-sectional, case–control	EDS support group: UK Established HSD/hEDS and hypermobility spectrum disorder: *n* = 616 (573 female); mean age 39 years PoTS *n* = 231 20% survey response	PoTS *vs* non-PoTS: functional esophageal disorders: 66% *vs* 50% (*P* < 0.001); functional heartburn: 31% *vs* 21% (*P* = 0.007); functional dysphagia: 51% *vs* 37% (*P* = 0.001); functional gastroduodenal disorders: 75% *vs* 67% (*P* = 0.04); functional dyspepsia: 68% *vs* 50% (*P* < 0.001); postprandial distress syndrome: 63% *vs* 42% (*P* < 0.001); epigastric pain syndrome: 40% *vs* 28% (*P* = 0.002); functional bowel disorders: 89% *vs* 91% (*P* = 0.5); IBS: 59% *vs* 51%; functional diarrhea: 3% *vs* 7% (*P* = 0.01); functional anorectal disorders: 60% *vs* 49% (*P* = 0.01)

†Villefranche criteria.[1]

population (54% *vs* 8%, *P* = 0.0001 in support group; 73% *vs* 16%, *P* = 0.001 in non-gastroenterology clinic setting).[5,27] Zweig *et al.* reported a higher prevalence of joint hypermobility (but not HSD/hEDS) in a cohort of constipation-predominant IBS compared with diarrhea-predominant IBS (58% *vs* 35%, *P* = 0.008) and found those with IBS and joint-hypermobility (not HSD/hEDS) were more likely to have concomitant postprandial distress (72% *vs* 49%, *P* = 0.007).[30] The data are even less clear when considering other functional bowel disorders, including functional constipation and functional diarrhea.[5,21,22,25] Similarly, the prevalence of functional anorectal disorders is variably reported[5,22,27,31] with, for example, no differences in patients referred to gastroenterology clinics with gastrointestinal symptoms (OR 1.79, CI 0.97–3.30, *P* = 0.06)[22] through to a much greater prevalence using Rome IV criteria in the UK support group (53% *vs* 9%, *P* < 0.0001).[5]

Importantly, the presence of HSD/hEDS with DGBI appears to be associated with greater overall impact in terms of healthcare

Table 3 Overview of the key findings generated from studies based on patients attending gastroenterology clinics

Author	Study type, clinic setting	Patient cohort	Assessment	Key findings
Mohammed, *et al.*, 2010[50]	Retrospective cohort Gastroenterology clinic	Intractable constipation and rectal evacuatory dysfunction: *n* = 200 (joint hypermobile *n* = 65; 179 female, median age 53 years)	• Questionnaires: 5PQ, Rome III questionnaire for IBS, comprehensive bowel symptom questionnaire including constipation score and fecal incontinence score • Anorectal physiology studies	Cases *vs* controls: • Joint hypermobility: 33% (65/200) *vs* 14% (*P* = 0.0005) • Pelvic organ prolapse with or without surgical repair: 31% (20/65) *vs* 17% (23/135) (*P* = 0.04) Hypermobile *vs* non-hypermobile group: • Abdominal pain: 75% *vs* 53% (*P* = 0.003) • Use of digital rectal evacuation: 69% *vs* 50% (*P* = 0.009) • Laxative use: 55% *vs* 37% (*P* = 0.03) • Reduced squeeze increment pressures: 32% *vs* 19% (*P* = 0.05) • Incomplete rectal evacuation: 80% *vs* 59% (*P* = 0.004) • Anorectal anatomical abnormalities: 86% *vs* 64% (*P* = 0.001) including large functional rectocele (28% *vs* 14%, *P* = 0.03); extrinsic compression of anterior rectal wall (11% *vs* 1%, *P* = 0.006); incomplete rectal evacuation: 80% *vs* 59% (*P* = 0.004)
Zarate *et al.*, 2010[26]	Retrospective neuro-gastroenterology clinic	129 consecutive newly referred patients stratified by joint hypermobility status; subset of 21 patients confirmed with HSD/hEDS	• Symptom assessment • Joint hypermobility	49% (63/129) had generalized joint hypermobility: • Symptoms: abdominal pain (81%), bloating (57%), nausea (57%), reflux symptoms (48%), vomiting (43%), diarrhea (14%) • Compared with non-hypermobile patients: younger; more often female; more likely to have bloating (62% *vs* 46%, *P* = 0.05), reflux symptoms (56% *vs* 30%, *P* = 0.005), unexplained gastrointestinal symptoms (81% *vs* 41%, *P* < 0.0001)
Fikree *et al.*, 2014[4]	Prospective cross-sectional General gastroenterology clinic	Consecutive new referrals (16–70 years) stratified by HSD/hEDS status (Brighton criteria) (Total *n* = 552; HSD/hEDS = 372 Non-HSD/hEDS: *n* = 80 HSD/hEDS patients referred from rheumatology clinic (positive control): *n* = 44	• Questionnaires: gut symptoms (bowel disease questionnaire); psychopathology (SCL-90); autonomic symptoms (COMPASS): quality of life (SF-36) • Examination • Structured interview	Undiagnosed HSD/hEDS 33% (*n* = 180/552): • younger (41 years *vs* 44 years, *P* = 0.003); • more likely to be female (68% *vs* 55%, *P* = 0.002) • greater prevalence of heartburn (aOR 1.66, CI 1.1–2.5); waterbrash (aOR 2.02, CI 1.3–3.1); postprandial fullness (aOR 1.74, CI 1.2–2.6) adjusting for age and sex

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Table 3 (Continued)

Author	Study type, clinic setting	Patient cohort	Assessment	Key findings
				Non-HSD/hEDS *vs* new HSD/hEDS *vs* previously diagnosed HSD/hEDS: • DGBI prevalence: 48% *vs* 58% *vs* 91% ($P < 0.001$) • Organic disorders: 44% *vs* 31% 8% ($P < 0.001$) • Autonomic symptom scores: urinary (0 *vs* 10 *vs* 30 ($P < 0.001$); orthostatic intolerance (25 *vs* 31.25 *vs* 68.75, ($P < 0.001$); vasomotor (0 *vs* 0 *vs* 56.7 ($P < 0.001$)
Fikree *et al.*, 2015[22]	Prospective case–control (functional and organic diagnosis) Secondary gastroenterology clinic	Consecutive referrals of patients with gastrointestinal symptoms, no prior HSD/hEDS diagnosis Total $n = 641$ (Organic disease controls $n = 306$ *vs* DBI cases $n = 336$; 378 female; mean age 42 years)	• Questionnaires: bowel disease questionnaire, pscyhopathology SCL-90; autonomic symptoms (COMPASS), somatic symptoms (PHQ-15) and quality of life (SF-36); • Structured interview and examination for HSD/hEDS (Brighton criteria) and fibromyalgia (1990 Wolfe criteria)	DGBI *vs* organic disease controls: • Female: 66% *vs* 52% ($P < 0.001$) • Mean age: 40 *vs* 44 years ($P = 0.001$) • HSD/hEDS prevalence: 39% *vs* 28% ($P = 0.002$) Adjusted OR (age, gender) for HSD/hEDS: • Functional gastroduodenal disorders (2.08, CI 1.25–3.46, $P = 0.005$); • Postprandial distress syndrome (1.99 CI 1.0–3.76, $P = 0.03$) • No association with lower gastrointestinal symptoms, including IBS DGBI-HSD/hEDS *vs* non-HSD/EDS: • Chronic pain: 23.2 *vs* 11.9 ($P = 0.02$), • Fibromyalgia: 10.5 *vs* 3.1 ($P = 0.01$),Somatic sensitivity: PHQ15 score 13 *vs* 10 ($P < 0.001$) • Anxiety: 0.5 *vs* 0.3 ($P = 0.01$); • Poorer quality of life scores (in domains of role-limiting emotional and pain)
Fikree *et al.*, 2017[43]	Retrospective, observational Neuro-gastroenterology clinic	Consecutive HSD/hEDS patients referred to gastrointestinal physiology unit for assessment of reflux or dysphagia HSD/hEDS: $n = 30$ (28 female; median age 30 years)—further stratified by PoTS status; non-HSD/hEDS dysphagia: $n = 98$ (56 female) Reflux controls: $n = 108$ (61 female)	• Questionnaires: reflux disease questionnaire, hospital odynophagia dysphagia questionnaire, Hospital Anxiety and Depression Scale (HADS) • Medical and medication history • High resolution manometry or multichannel intraluminal impedance testing	HSD/hEDS *vs* non-HSD/hEDS: • Reflux hypersensitivity (21% *vs* 5%, $P = 0.01$). • Esophageal hypomotility 40% in HSD/hEDS *vs* 23% in ($P = 0.09$). PoTS *vs* non-PoTS-HSD/hEDS: • Reflux scores: 24.5 *vs* 16.5 ($P = 0.05$) • Dysphagia scores: 21 *vs* 11.5 ($P = 0.04$)

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Table 3 (Continued)

Author	Study type, clinic setting	Patient cohort	Assessment	Key findings
Menys *et al.*, 2017[54]	Pilot feasibility Tertiary neuro-gastroenterology clinic	HSD/hEDS with Postprandial distress (Rome III): *n* = 9 Healthy controls: *n* = 9	• MRI at baseline following cessation of motility-influencing medication • Gastric emptying time, motility and accommodation and duodenal distension and motility assessed following ingestion of water.	HSD/hEDS *vs* control: • Similar gastric emptying time: 12.5 *vs* 20 min ($P = 0.15$). • Lower mean increase in gastric motility: 11% *vs* 22% ($P = 0.03$). • Similar gastric accommodation: 56% *vs* 67% ($P = 0.19$)
Zweig *et al.*, 2018[30]	Retrospective review of prospectively collected data at neuro-gastroenterology clinic	228 IBS (Rome III) patients (67% female); stratified by joint hypermobility status	• Rome III criteria • Beighton score and Brighton criteria • Psychological assessment: visceral sensitivity index; Hospital and Anxiety Depression Scale	Joint hypermobility • More common in female *vs* male: 83 (55%) *vs* 12 (16%) $P < 0.001$ • Significantly higher in IBS-C compared with IBS-D (58% *vs* 35%, $P = 0.008$) • IBS patients reported significantly more concomitant postprandial distress: 72% *vs* 49%, $P = 0.007$ • Similar visceral sensitivity index 38 *vs* 37, $P = 0.720$ • No significant association between HSD/hEDS and IBS subtypes
Carbone *et al.*, 2021[55]	Prospective case–control University hospital clinic	Functional dyspepsia (Rome III): *n* = 39 stratified by HSD/hEDS status using Brighton classification Healthy controls: *n* = 15	• Questionnaire: dyspepsia symptom severity score; visual analogue scale • Blinded nutrient drink infusion via nasogastric tube at 60 ml/min until satiation or symptoms • Intragastric pressure measured by high resolution manometry	HSD/hEDS *vs* controls • Functional dyspepsia: 56% *vs* 7% ($P = 0.002$) • No differences in symptom pattern
Carbone, *et al.* 2022[61]	Retrospective recruitment, prospective evaluation of joint hypermobility Gastroenterology clinic	62 patients with preexisting functional dyspepsia *n* = 62 (68% female, age 44 years, BMI 22 kg/m^2)	• Interview and examination for HSD/hEDS status (Brighton criteria) • Historic results for gastric emptying (using ^{13}C breath test); gastric barostat assessment	55% HSD/hEDS criteria met *vs* 39% no joint disease/syndrome *vs* 6% "other" joint disorder HSD/hEDS *vs* non-HSD/hEDS • Female: 74% *vs* 63% ($P = 0.02$) • Similar symptomatology: postprandial fullness (76% *vs* 82%); bloating (73% *vs* 77%); early satiety (58% *vs* 41%); nausea (42% *vs* 36%); belching (42% *vs* 36%); reflux (21% *vs* 5%) • Similar rates of delayed gastric emptying (32% *vs* 16%, $P = 0.31$) • No differences in gastric compliance, minimal distention pressure and meal-induced proximal stomach relaxation

utilization, quality of life, somatic symptoms and the extent of gastrointestinal involvement, compared with respondents meeting criteria for DGBI alone.[5,22] Individuals with comorbid HSD/hEDS and DGBI report more frequent experiences of pain (23% *vs* 12%, $P = 0.01$), worse pain-related quality of life scores (45 *vs* 63.5, $P = 0.004$), comorbid diagnosis of fibromyalgia (11% *vs* 3%, $P = 0.01$), higher somatization scores (13 *vs* 10,

$P < 0.001$) and higher anxiety scores (0.50 *vs* 0.30, $P = 0.01$) compared with non-HSD/hEDS DGBI patients.[22]

Organic gastrointestinal disease. There is a paucity of studies exploring associations between HSD/hEDS with organic

gastrointestinal conditions although potential links have been identified.

Celiac disease. The potential association between celiac disease and HSD/hEDS was initially proposed after 5 of 31 Italian patients with HSD/hEDS (16%) had celiac disease, considerably more than might be anticipated from the background prevalence of about 1%.[32] Subsequent interrogation of a large population-based Swedish registry identified a significant association of HSD/hEDS with histologically proven celiac disease (14 *vs* 9 per 100 000 person-years with a hazard ratio of 1.49, 95% CI, 1.07–2.07, $P = 0.018$).[33]

Crohn's disease. Joint hypermobility (using the Beighton score alone) has been observed more frequently in patients with Crohn's disease with 29 of the 41 Crohn's patients (71%) having joint hypermobility compared with 10 of the 28 patients (36%) with ulcerative colitis ($P = 0.006$) and 17 of the 67 age-matched and sex-matched healthy controls (25%) ($P < 0.0001$).[34] Furthermore, the prevalence of HSD/hEDS (using the Brighton criteria) followed similar trends (12% in Crohn's disease *vs* 4% in ulcerative colitis [OR 3.75, 95% CI: 0.41–34.0]).[34] In another cohort, HSD/hEDS was present in 8 of 25 patients with Crohn's disease (32%) and 8 of 38 patients (21%) with ulcerative colitis.[22]

Other gastrointestinal diseases. There are no signals for an increased risk of gastric or colorectal neoplasia or of complications related to diverticular disease in patients with HSD/hEDS although formal studies are lacking. The prevalence of diverticular disease, similarly, has not been systematically assessed. In the only relevant report, a study of issues associated with colonoscopy such as safety and post procedure pain, 22 of 200 patients met criteria for HSD and that sub-group had a similar prevalence of polyps (27% *vs* 41%, respectively; $P = 0.2$) and diverticulosis (39% *vs* 36%, $P = 0.7$) as those without HSD.[35] Other studies have reported rates of diverticular disease of 10–13% and rates of polyps of 8–23%. However, these data are drawn from retrospective chart reviews of patients who were not systematically evaluated and so the generalizability of these figures is uncertain.[14,36]

Liver disease. While "at-risk" alcohol consumption has been reported to occur more often in patients with joint hypermobility (not hEDS specifically), there have been no data suggesting a higher incidence of chronic liver disease in the HSD/hEDS population.[37,38] One case–control study conducted from a rheumatology clinic reported an association between unconjugated hyperbilirubinemia from Gilbert's syndrome and hypermobile joints.[39] However, the reason these patients were referred to the rheumatology clinic in the first instance was not examined and the source of recruitment of the control group was not reported, which may limit the generalizability of the conclusions.

Pathophysiological contributors to gastrointestinal symptoms in HSD/hEDS

An understanding of the current status of the pathophysiological basis for gastrointestinal and other symptoms in patients with

HSD/hEDS is valuable in counseling the patients. There are multiple hypotheses and potential explanations that largely fall into three categories—the anatomical effects of connective tissue laxity and weakness *per se*, their functional consequences, and the influence of non-gastrointestinal issues that include autonomic dysfunction, medication effects or comorbid mental health disorders. The current evidence base supporting these proposed hypotheses remains limited.

Anatomical variation/abnormalities. A variety of anatomical abnormalities related to increased connective tissue laxity and weakness have been observed.[40] On first principles, it seems reasonable that such abnormalities might be associated with symptoms. Specific abnormalities include the following:

- *Hiatus hernia*: The prevalence of hiatus hernia in HSD/hEDS has been variably reported, as high as 58%.[41] Other studies, however, have shown it to be similar to the background population (8–26% in HSD/hEDS *vs* 2–22% general population) suggesting hiatus hernia may not be the main mechanism responsible for the commonly reported symptom of reflux.[14,28,42–44] It has been postulated that there is laxity of the gastro-hepatic and phreno-esophageal ligaments in patients with HSD/hEDS, providing a basis for the reported association. This hypothesis is supported by the observed depletion of elastic fibers in those ligaments of patients with gastroesophageal reflux disease and hiatus hernia, although these patients were not assessed for underlying HSD/hEDS.[45]

- *Visceroptosis*: Abnormal connective tissue leading to altered fixation of viscera to the peritoneum has been implicated in the development of visceroptosis (defined as sinking of an organ below its normal position) of various organs in case reports of patients with HSD/hEDS.[46–49] The relationship between the structural change and clinical presentation has not been well-defined.

- *Pelvic organ prolapse*: This occurs about twice as often in patients with HSD/hEDS compared with non-HSD/hEDS individuals. For example, in a case–control study of 60 females referred to a tertiary hypermobility clinic, 73% had clinically-significant prolapse compared with 35% of the age-matched and sex-matched healthy controls ($P < 0.001$).[31] These individuals were also more likely to experience symptoms of obstructive defecation on questioning (23% *vs* 5%, $P = 0.007$).[31] Likewise, more patients with rectal evacuatory dysfunction reported a history of pelvic organ prolapse (with or without surgery) in the HSD/hEDS cohort compared with the non-HSD/hEDS group (31% *vs* 17%, $P = 0.04$).[50] Objectively, anorectal anatomical abnormalities seen on proctography were more common in the HSD/hEDS group compared with the non-HSD/hEDS cohort (86% *vs* 64%, $P = 0.001$), specifically for large functional rectoceles (28% *vs* 14%, $P = 0.03$) and extrinsic compression of the anterior rectal wall from an enterocele or the uterus (11% *vs* 1%, $P = 0.006$). Higher frequencies of reduced squeeze increment pressures (32% *vs* 19%, $P = 0.05$) and incomplete rectal evacuation (80% *vs* 59%, $P = 0.004$) compared with the non-HSD/hEDS controls were also seen. No differences in rectal sensation or frequency of reduced anal resting tone

were noted.[50] Fikree *et al.* also described a higher incidence of organ prolapse in their study, which increased statistically significantly by HSD/hEDS status.[4] Despite this, the clinical significance of these findings is difficult to interpret given the lack of control data and the relatively common finding of anatomical variations like prolapse in asymptomatic subjects.[50]

- **Short-segment intussusception**: This is postulated to arise secondarily to altered tensile strength of hollow viscera leading to excessive visceral distension in combination with altered fixation of the viscera to the peritoneum in patients with HSD/hEDS. However, the prevalence of intussusception in both the HSD/hEDS and general populations remains unknown and the mechanistic relationship of short-segment intussusception to gastrointestinal symptoms, such as abdominal pain and bloating, is poorly understood. There was no observed difference in the prevalence of rectal intussusception, which presumably has similar pathophysiological mechanisms, in the study of rectal evacuatory dysfunction in patients with and without HSD/hEDS (41% *vs* 39%, *P* = 0.76).[51]

- **Dolichocolon (elongation or redundancy of the colon)**: Such an anatomical variant may predispose patients to volvulus, abdominal pain or constipation. To date this has not been substantiated by evidence as a potential mechanism in HSD/hEDS.[40,52]

Altered gastrointestinal tract function. There are several interrelated aspects to potential alteration of gastrointestinal function:

- **Altered compliance of the gastrointestinal tract wall and changes in mechanoreceptor function**: Increased elasticity (compliance) of the gastrointestinal wall will manifest as increased distension from a given intraluminal force. Thus, theoretically, a given amount of luminal gas in a patient with altered connective tissue arising from HSD/hEDS may yield greater intestinal distension and subsequent mechanoreceptor stimulation than a person without HSD/hEDS. Because luminal wall stretch is a major stimulus to inducing pain and bloating, it might be anticipated that patients with HSD/hEDS will be more susceptible to symptom induction following gaseous distension.[53] Neither colonic compliance nor gut mechanoreceptor function in the hEDS population have been measured to test this hypothesis although no changes in gastric accommodation have been observed in HSD/hEDS studies of functional dyspepsia using MRI or intragastric barostat measures, arguing against this hypothesis.[54,55]

- **Dysmotility**: Following on from the aforementioned hypothesis, altered wall compliance/elasticity and mechanoreceptor function also influences gastrointestinal motility. Studies in murine and guinea pig models show that enteric neurons are activated or inhibited by luminal stretch with resultant motility changes.[56] This hypothesis is supported by studies in the IBS population following luminal gas infusion, in which objective abdominal distension and subjective reporting of abdominal symptoms appear to be more related to an altered motility response (poor gas transit) than to increased gas volume.[57,58] It is possible a similar process predominates in hEDS. In support of this, gastric MRI revealed altered motility in response to water ingestion in HSD/hEDS patients with functional dyspepsia compared with healthy controls.[54] Other studies of gastric sensorimotor function, compliance and emptying in small cohorts of patients with HSD/hEDS have otherwise revealed few specific abnormalities.[14,26,29,36,43,54,55] Similarly, colonic transit studies have also revealed no specific abnormalities in HSD/hEDS patients.[14,26,36,50]

- **Visceral hypersensitivity**: Direct alterations in neuronal function leading to visceral hypersensitivity have also been proposed as a contributor for symptoms in hEDS. A number of hypotheses have been proposed. First, tenascin-X, a glycoprotein component of extracellular matrix for which a genetically-driven deficiency, has been rarely linked with HSD/hEDS, plays a role in the neural control of colonic sensory and motor function. This has also recently been shown to play a role in upper gastrointestinal function.[59,60] TNX deficiency in mice has been shown to correlate with increased sensitivity of vagal afferent nerves to gastric distension and associated with accelerated gastric emptying.[60] Nevertheless, the correlation between gastric emptying and symptoms in functional dyspepsia has not been borne out in studies in non-HSD/hEDS cohorts, which limits the conclusions that can be drawn.[61] Secondly, α-2 adrenergic activity plays a role in visceral sensitivity in healthy volunteers and could potentially play a role in connective tissue disorders, although this has not been specifically studied in the HSD/hEDS population.[62] Thirdly, central sensitization, as seen with generalized, chronic widespread pain, will secondarily promote visceral hypersensitivity.[13] This hypothesis is supported by a greater prevalence of reflux hypersensitivity (high-resolution manometry and pH manometry) in patients with upper gastrointestinal symptoms in those with and without HSD/hEDS (21% *vs* 5%, *P* = 0.01).[43]

- **Altered vascular compliance**: Venous pooling in the lower limbs has been described in HSD/hEDS related to altered connective tissue of blood vessels and has been proposed to contribute to cardiovascular and autonomic symptoms present in HSD/hEDS patients. Alterations in splanchnic circulation may also be expected and could contribute to the gastrointestinal symptoms experienced.

Non-gastrointestinal mechanisms. HSD/hEDS is characterized by a number of non-musculoskeletal manifestations (Figs 2 and 3) which can contribute to the patient's presentation to a gastroenterologist. Three important factors are proposed to contribute: autonomic dysfunction, effects of medications, and mental health disorders, including eating disorders.

- **Autonomic dysfunction**: The autonomic nervous system plays a key role in maintaining homeostasis in the body, with roles in fluid balance, temperature regulation and blood pressure. Symptoms of autonomic dysfunction can include presyncope, orthostatic intolerance, chest pain, palpitations, thermoregulatory difficulties, and gastrointestinal complaints

and are commonly reported in patients with HSD/hEDS.[63–65] For example, they are almost three times more likely than healthy controls to experience presyncopal symptoms (41% *vs* 15%) and experience orthostatic intolerance frequently (94% of HSD/hEDS in one study).[15,63,65]

Cardiovascular autonomic dysfunction can include orthostatic hypotension, orthostatic intolerance, neurally-mediated hypotension and postural orthostatic tachycardia syndrome (PoTS), the latter of which is commonly associated with HSD/hEDS.[66] PoTS is a heterogeneous syndrome that is manifested by a rapid increase in heart rate (> 30 bpm in adults) within 10 minutes of changing from recumbent to upright position without orthostatic hypotension.[67] Multisystemic involvement is common, with gastrointestinal symptoms (including nausea, irregular bowel movements, abdominal pain, bloating and constipation) the most frequent non-cardiovascular symptoms reported.[68,69] The cause for these symptoms is likely to be multifactorial, but may be related to changes in splanchnic circulation, presence of small fiber neuropathy or altered vascular compliance related to the generalized tissue laxity in hEDS.[68,69] The prevalence of PoTS in HSD/hEDS cohorts ranges from 15% to 41%.[36,63,64,70–72] The prevalence of hEDS also appears to be higher in PoTS cohorts compared with the general population, with 31% of PoTS patients meeting the 2017 diagnositc criteria for hEDS.[72]

The clinical association between HSD/hEDS and PoTS is noted, but their relationship remains unclear. There is some evidence that the copresence of the two disorders may represent a more severe disease phenotype.[36,43,70,71] For example, studies have shown that symptoms of gastroesophageal reflux and dysphagia are worse, esophageal hypomotility more marked and pathological gastroesophageal reflux disease more severe in those with comorbid HSD/hEDS and PoTS compared with HSD/hEDS alone.[43] Abnormal gastrointestinal motility is also more than five times likely,[36] and the burden of DGBI is greater.[71] Cohorts of patients with comorbid PoTS and HSD/hEDS appear to be younger than either alone, suggesting that the symptoms become apparent at an earlier age or perhaps present more severely leading to earlier diagnosis.[67,71]

- *Medication effects*: Patients with HSD/hEDS report high regular medication use, with opiates being potentially the most troublesome from a gastrointestinal perspective. Up to 92% of HSD/hEDS respondents in one study reported regular medication use of which analgesics were the most common.[12] Polypharmacy is also prevalent, with an average of three medications per patient reported and chronic opiate use seen in over one third of HSD/hEDS patients.[12] While Fikree *et al.*'s studies did not find any association between gastrointestinal symptoms or esophageal dysmotility and opiate use, the widespread actions of opiates on multiple aspects of gastrointestinal function and their established side effect profile including constipation, nausea, vomiting and pain sensitization means they cannot be ignored.[4,43,73] Other potential pharmaceutical contributors such as antidepressants, are used by 15–27% of HSD/hEDS patients. These medications also have vasoactive properties, effects on

autonomic function and a range of gastrointestinal side effects.[4,65,74]

- *Mental health contributors*: There is a recognized increased prevalence of mental health disorders in patients with HSD/hEDS, including anxiety and depression.[38,75–77] In a retrospective survey of 391 patients with a diagnosis of mostly HSD (80%) or EDS (notably no hEDS), almost half of the respondents were affected by a psychiatric disorder and almost 30% described two or more simultaneous psychiatric diagnoses.[75] Significant associations were noted between gastrointestinal dysfunction and mood disorders (OR 2.07, 95% CI 1.33–3.25, $P = 0.001$), depression (OR 1.68, 95% CI 1.07–2.66, $P = 0.026$), somatoform disorders (OR 2.61, 95% CI 1.62–4.19, $P < 0.001$) and anxiety (OR 2.26, 95% CI 1.39–3.67, $P < 0.001$). In a long term population cohort study with 15 years of follow up, those patients with HSD/hEDS defined by Brighton criteria performed at the time of recruitment (29 of the 137 subjects) had a relative risk of panic disorder or agoraphobia 22 times greater than that of the non-HSD/hEDS patients.[18] There is also increasing interest in the association between HSD and neurodevelopmental disorders, including attention-deficit/hyperactivity-disorder and autism spectrum disorder.[17]

- *Disordered eating and HSD/hEDS*: There are multiple reasons patients with HSD/hEDS might modify their eating patterns. Oral mucosal fragility, temporomandibular dysfunction, masticatory muscular problems and dental issues, such as poor dentition or overcrowding of the teeth may lead to altered oral intake.[2,78,79] Patients with hEDS may also experience enhanced interoception (heightened awareness of bodily information and stimuli), somatosensory amplification and have underlying chemosensory disorders (involving smell and taste changes), influencing oral intake and the development of food aversions.[79] Finally, and unrelated to HSD/hEDS itself, is that modification of diet is common in patients with DGBI, where food type and quantity is altered by perceived food intolerances as a strategy to minimize symptoms such as bloating.[80]

Differentiating a primary eating disorder from disordered eating patterns related to the aforementioned factors can be challenging in patients with HSD/hEDS.[81] A weak association of eating disorders with EDS, based upon theory and case reports, is noted but formal studies are limited.[79] Awareness of such diagnostic challenges is critical to managing these patients who are often young females, with anorexia, low body weight and significant gastrointestinal symptoms. The consequences of weight loss and poor nutrition should also not been overlooked as these may worsen the natural history of hEDS by contributing to physical deconditioning, reduced bone mass, fatigue, and poor quality of life.[79,82]

Management considerations

There is a general lack of evidence to guide therapeutic approaches for patients with HSD/hEDS. Indeed there is also no single approach that will fit all HSD/hEDS patients, given the various combinations of manifestations that may be present. Management is largely supportive in nature and symptom-focused, and often

Table 4 Checklist for a patient presenting with gastrointestinal symptoms potentially associated with HSD/hEDS

Actions	Notes
Screen patients for hEDS with 5-point questionnaire	• 5-point questionnaire[10]
	1. *Can you now (or could you ever) place your hands flat on the floor without bending your knees?* **2.** *Can you now (or could you ever) bend your thumb to touch your forearm?* **3.** *As a child, did you amuse your friends by contorting your body into strange shapes, or could you do the splits?* **4.** *As a child or teeenager did your shoulder or kneecap dislocate on more than one occasion?* **5.** *Do you consider yourself double-jointed?*
Exclusion of organic gastrointestinal conditions	• Consider new diagnosis of hEDS in patients with multisystemic symptoms and DGBI • Early referral to multi-disciplinary teams if available • Screening for celiac disease (e.g. celiac-specific serology if consuming gluten) and inflammatory bowel disease (e.g. fecal calprotectin, colonoscopy if high suspicion) as recommended in any patient with chronic gastrointestinal symptoms • In patients with Crohn's disease, consider HSD/hEDS overlap with spondyloarthropathy[34] • Judicious use of investigations and procedures to minimize duplication of care and iatrogenic risk from low yield procedures. Endoscopic procedures should be performed on their clinical merits. No evidence of increased procedural risks (perforation, post-procedural pain in HSD; possible increased risk of bleeding in hEDS patients with minor bleeding disorder)
Institute integrated management for DGBI symptoms	Evidence for management specifically in HSD/hEDS lacking–attention to: • Integrated care and behavioral therapies[85] • Dietary management: FODMAP diet efficacious in HSD/hEDS-related DGBI[89] • Pelvic floor dysfunction: consider early referral for anorectal physiological assessment and biofeedback/pelvic floor physiotherapy • Psychology input to address psychological comorbidity
Consider nutritional and dietary issues	• Assess nutritional status as undernutrition is common and multifactorial[79] • Optimization of bone health: vitamin D and calcium supplementation as required • Screen for weight loss and disordered eating patterns (dietitian) • Consider the following ○ Underlying eating disorder, in particular avoidant/restrictive food intake disorder (ARFID) ○ Dental and oral mucosal health, temporomandibular joint (dys)function ○ Presence of underlying chemosensory disorder (altered taste and smell) ○ Alteration of diet due to presence of DGBI symptoms ○ Consider the impact of eating disorder itself on gastrointestinal function (e.g. generation of IBS-like symptoms, constipation, postprandial fullness, bloating, and early satiety)[81]
Address extra-intestinal manifestations—consider referral to appropriate healthcare professional	• Increased risk of psychiatric comorbidities • Increased risk of 'at risk' substance use (alcohol, tobacco) • Musculoskeletal involvement often widespread, affecting joints beyond those listed in diagnostic criteria • Chronic pain syndromes common—individualized pain management appropriate, awareness of opiate use • Chronic fatigue symptoms common—multidisciplinary approach[84] • Consider contribution of autonomic nervous system-related symptoms • Consider physical deconditioning, which may exacerbate autonomic dysfunction and musculoskeletal symptoms, fatigue and pain • Consider referral to cardiologist for surveillance in those with positive family history of cardiac/aortic disease or abnormal cardiovascular clinical examination findings on auscultation; no clear guideline regarding routine/baseline echocardiographic surveillance[2,90]
Pharmacological considerations	• Consider the effects of medication on symptoms (e.g. fatigue, sleep quality, and gastrointestinal dysfunction) • Caution with opiates, particularly in those with gastrointestinal symptoms
Support	• Referral to support group/local hEDS organization • Providing patients with pathways to obtain further information about the condition and allow family members to consider this diagnosis where appropriate
Professional education and training	• Further healthcare professional training is available through EDS Society (EDS ECHO), established 2019 with evidence for improved outcomes and physician confidence[20]

recommended on the basis of prior clinical experience or using strategies adapted from management of "similar" patient groups. We have proposed a suggested "hEDS checklist" that could be followed in defining therapeutic strategies in patients with hEDS who are presenting with gastrointestinal symptoms (Table 4). Awareness of the multiple pathways by which such symptoms can arise is important in order to provide the best individualized treatment. If standard therapies fail, alternative etiologies for the symptoms should be considered.

Awareness of HSD/hEDS. The presentation of HSD/hEDS varies greatly between individuals and thus the diagnosis is often delayed, referred to as the "diagnostic odyssey."[83] Greater awareness of HSD/hEDS among physicians may enable an earlier diagnosis and more timely uptake of integrated, multidisciplinary care providing holistic and expert support for the various systems potentially affected. This process is particularly important given that few centers offer multi-specialty HSD/hEDS clinics. Additional benefits of this approach might include reduced healthcare utilization and costs associated with numerous medical consultations, investigations, unnecessary surgeries and other interventions, treatment regimens and time off work. It is also important to avoid the incorrect use of the label "hEDS." Clear diagnostic criteria should be used and patient education facilitated by a sound working knowledge of the hypermobility spectrum disorders and their diagnostic limitations.

Integrated care. While evidence for timely, collaborative care is limited in the HSD/hEDS population, integrated care of patients with irritable bowel syndrome and other DGBI have been shown to improve health-related quality of life, patient psychological wellbeing and other outcomes.[84,85] Given the complexity of the multisystemic issues that often present in patients with HSD/hEDS, care of highly symptomatic patients may require collaborative input from various health professionals including (but not limited to) general practitioners, physicians (e.g. gastroenterology, cardiology, and rheumatology), psychiatrists and psychologists, chronic pain specialists, dietitians, physiotherapists/exercise physiologists, and dentists.

Safety with surgery and endoscopy. Patients and doctors alike may express concern regarding the safety of endoscopic and surgical procedures in patients with connective tissue and autonomic problems. Indeed orthopedic complications are known to be higher in HSD/hEDS. However, in general, the risks of severe adverse procedural outcomes are low in HSD/hEDS.[40] General considerations, however, may include: anesthetic risks (including circulatory management in patients with autonomic dysfunction, temporomandibular joint subluxation/dislocation or cervical spine instability); history of bruising and tissue fragility; hyperextension/force on joints at risk of dislocation or subluxation when the patient is being mobilized; and the procedural risks themselves.[40,86]

Symptoms will dictate the need for a colonoscopy and/or upper gastrointestinal endsocopy in many patients. The risk of perforation does not appear to be increased. This is in contrast to patients with vascular EDS in whom vascular and visceral perforation risk

is high.[87] Procedural difficulty has been theorized to be more challenging due to the presence of hernias and increased laxity of the colon, but has not been verified in studies.[35] Indeed endoscopist-reported difficulty and cecal intubation rates are not dissimilar between HSD and non-HSD cohorts.[35] There does not appear to be a significantly greater rate of post-procedural pain.[35] Increased risk of bleeding in association with colonoscopy has not been reported but should be assessed in the context of the patient's personal history of bleeding (which may be increased) and the planned procedure, particularly in those with mast cell activation syndrome.[88] Laboratory results are usually within normal range.[88]

Familial screening. There are currently no formal guidelines on familial screening. However, family history is a component of the new diagnostic criteria and the syndrome is believed to be inherited in an autosomal dominant manner with incomplete penetrance, which makes screening family members a relevant consideration. The spectrum of the disorder means that family members may present with their own unique manifestations and remain undiagnosed despite meeting the criteria. As there is no diagnostic molecular marker known, referrals to genetics clinics are likely to be managed variably according to local practices and based on waitlists and availability. Recommendations regarding familial echocardiographic screening are best determined by the treating cardiologist as the understanding of the natural history of cardiovascular abnormalities in HSD/hEDS continues to evolve.

Future research directions. The key impediment to progress in improving the diagnosis and understanding of the clinical manifestations of this spectrum of disorders is the identification of the genetic basis (es) to HSD/hEDS. In the absence of such objective markers, evaluation of the more stringent 2017 International Classification of the EDS is needed in order to clarify the many areas of imprecision and to minimize inaccurate and somewhat emotive attribution of many illnesses to the underlying connective tissue disorder. The same applies to how gastrointestinal anatomy and physiology are altered in hEDS, and how (and if) these relate to the intestinal and extra-intestinal manifestations observed in hEDS. Consideration of the complex interaction between the gut, brain, other organs and the environment (including medication), and how these may alter the susceptibility of a patient to the development of abdominal symptoms, also needs further consideration. Greater understanding of pathophysiological processes will then allow more targeted treatment strategies with integrated care to be studied and implemented.

Conclusions

All general gastroenterologists will encounter patients with (diagnosed or undiagnosed) HSD/hEDS. Recognition of such patients and a general understanding of the implication of such a disorder will provide the opportunity for timely and reassuring explanation, for arranging multidisciplinary care as required, and minimizing inappropriate investigations and therapies. In this way, gastroenterologists have the opportunity to improve the long term outcomes of these patients.

Acknowledgment

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Supporting information

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

Table S1 2017 International classification of the Ehlers-Danlos syndromes including key clinical features, prevalence, genetic basis and gastrointestinal involvement.[7,91]