Rome IV Functional Gastrointestinal Disorders and Health Impairment in Subjects With Hypermobility Spectrum Disorders or Hypermobile Ehlers-Danlos Syndrome

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Title: Rome IV Functional Gastrointestinal Disorders and Health Impairment in Subjects With Hypermobility Spectrum Disorders or Hypermobile Ehlers-Danlos Syndrome

Abstract:

Background & Aims: Individuals with hypermobility spectrum disorder or hypermobile Ehlers-Danlos Syndrome (HSD/hEDS) are increasingly encountered by gastroenterologists and pose complex clinical challenges. Uncontrolled studies have found functional gastrointestinal disorders (FGIDs) to be common in patients with HSD/hEDS. Some patients have somatic symptoms (medically unexplained symptoms) that might affect FGIDs. We performed a case–control study to determine the prevalence of and factors associated with Rome IV FGIDs in subjects with HSD/hEDS compared with age- and sex- matched population-based controls.

Methods:An online general health survey was completed by 603 individuals with HSD/hEDS in October 2018 (cases) and 603 matched individuals from the population of the United Kingdom (controls) in 2015. The mean participant age was 39 yrs, and 96% were women. The survey included questions about Rome IV FGIDs, non-GI and non-musculoskeletal somatic symptoms (maximum number, 10), quality of life, medical history and healthcare use. The prevalence of FGIDs was compared between cases and controls, with subsequent logistic regression models - adjusting for the number of somatic symptoms - used to determine the associations for FGIDs in HSD/hEDS compared with controls.

Results: Nearly all subjects (98%) with HSD/hEDS fulfilled symptom-based criteria for 1 or more Rome IV FGIDs, compared with 47% of controls (*P*<.0001). The gastrointestinal regions most commonly affected by FGIDs in individuals with HSD/hEDS and control subjects were the bowel (90% vs 40% of controls), gastroduodenal (70% vs 13% of controls), esophageal (56% vs 6% of controls), and anorectal (53% vs 9% of controls); *P*<.0001. A higher proportion of subjects with HSD/hEDS had FGIDs in 2 or more regions (84% vs 15% of controls; *P*<.0001). Subjects with HSD/hEDS also reported a significantly higher number of non-GI and non-musculoskeletal somatic symptoms (7.1 vs 3.3 in controls), lower quality of life, and greater healthcare use, including abdominal surgeries and medication use (for example, 84% used analgesics compared with 29% of controls). Almost 40% of subjects with HSD/hEDS reported a diagnosis of chronic fatigue syndrome and/or fibromyalgia. Following adjustments for somatic symptoms, the association for FGIDs in subjects with HSD/hEDS was reduced by as much as 4-fold and in some instances was eliminated.

Conclusions: In a large case–control study of persons with HSD/hEDS, almost all of the cases met criteria for Rome IV FGIDs, incurred considerable health impairment, and had high healthcare use. Patients with HSD/hEDS frequently have somatic symptoms that should be treated to reduce the high burden of gastrointestinal illness in this population.

KEY WORDS: joint hypermobility syndrome, QoL, overlap, abdominal

WHAT YOU NEED TO KNOW

Background: Individuals with hypermobility spectrum disorder or hypermobile Ehlers-Danlos Syndrome (HSD/hEDS) are increasingly encountered by gastroenterologists. Little is known about the prevalence of and factors associated with functional gastrointestinal disorders (FGIDs) in patients with HSD/hEDS.

Findings: In a large case–control study of persons with HSD/hEDS, almost all of the subjects met criteria for Rome IV FGIDs, incurred considerable health impairment, and had high healthcare use.

Implications for patient care: Healthcare providers should aim to control somatic symptoms in patients with HSD/hEDS to reduce FGIDs and other life-impairing co-morbidities.

Introduction:

Generalised joint hypermobility affects 10-20% of the population and is characterised by the ability to actively or passively move joints beyond normal limits.[1] The vast majority with joint hypermobility are asymptomatic and in these it is considered a benign, harmless trait. Indirect evidence suggests that around 3% of the population have hypermobility spectrum disorders (HSD), previously known as joint hypermobility syndrome, defined as musculoskeletal symptoms in a hypermobile individual in the absence of systemic rheumatological disease.[1] However, HSD may be blurred with hypermobile Ehlers-Danlos Syndrome (hEDS), a rare systemic connective tissue disorder affecting approximately 1-in-5000 people, due to their overlapping criteria being implemented outside specialised centres and the absence of an objective diagnostic biomarker. As such, many patient- and research- support groups use the terms HSD and hEDS interchangeably, which will also be the case in this article.

Whereas HSD/hEDS has traditionally been confined to rheumatology and pain clinics, the last decade has seen emerging data to suggest that individuals with HSD/hEDS are increasingly being encountered within gastroenterology services.[2-7] Some tertiary-care neurogastroenterology centres report that almost half of their new out-patient referrals are accounted for by HSD/hEDS, although arguably this may be an overestimation due to referral bias and/or the complex diagnostic criteria being applied by non-rheumatologists.[2,3] Nevertheless, these patients pose substantial therapeutic challenges to healthcare providers given the array of highly burdensome intestinal and extra-intestinal symptoms, of which chronic pain is often at the core of the most intrusive and debilitating clinical manifestations.[2] The majority of HSD/hEDS patients who present with gastrointestinal symptoms do not have organic pathology and are diagnosed as having a functional gastrointestinal disorder (FGID).[2-6] Indeed, studies report that FGIDs can be present in over 90% of subjects with HSD/hEDS, although such findings are limited to case-series, cohort studies, and a few small secondary-care case-control studies.[2-12] Moreover, the association between HSD/hEDS and FGIDs may be confounded by alternate factors, such as somatic symptoms which -defined as the tendency to report medically unexplained symptoms- have been documented in approximately 60% of HSD/hEDS subjects,[2] and are of importance for symptom severity in FGIDs.[13] To date, the prevalence and associations for FGIDs in subjects with HSD/hEDS has not been explored against a suitably matched population-based control group. Such an evaluation will help clarify the magnitude of gastrointestinal illness in HSD/hEDS and provide insight into identifying potentially modifiable risk factors to help alleviate the high symptom burden. It will also aid towards directing future clinical service and research provision in this patient group.

We performed a large case-control study addressing the prevalence and associations for Rome IV FGIDs in subjects with HSD/hEDS against age- and sex-matched general population-based controls. We hypothesised that FGIDs will be highly prevalent in HSD/hEDS, and that the presence of somatic symptoms will be a relevant confounder.

Materials and Methods

Study design and participants

In October 2018, an online general health questionnaire from our research group was sent out by the charity organisation Ehlers-Danlos Support UK to its 3874 contactable members. Following an e-mail reminder at two weeks, the survey was closed at one month. In total, 777 subjects completed the survey, giving a response rate of 20%. All subjects declared a medical diagnosis of Ehlers-Danlos Syndrome. However, the society allows its members to use the terms hEDS and HSD interchangeably; therefore, any subject with a supposed diagnosis of hEDS was re-classified as HSD/hEDS. Following exclusion of 161 cases for various reasons (82 inconsistent responders, 30 with subtypes other than HSD/hEDS, and 49 with co-existing organic gastrointestinal pathology; 28 coeliac disease, 22 inflammatory bowel disease, 2 gastrointestinal cancers) there were 616 subjects with HSD/hEDS who were eligible as the case group.

Our controls were selected from a nationally representative sample of 1994 population-based UK adults who had completed essentially the same survey in 2015, which at that time was used to determine the prevalence of FGIDs within the general population.[14] From this sample, 54 were excluded due to having an organic gastrointestinal pathology; 9 coeliac disease, 25 inflammatory bowel disease and 21 gastrointestinal cancers. This left 1940 population-based subjects who were eligible as the control group.

Following computer generated case-control matching for gender and age (+/- 2 years), the final dataset included 603 HSD/hEDS cases and 603 population-based controls; all were matched exactly for gender, with 91% (n=548) being of the same age and 9% (n=55) within 2 years.

Questionnaire

The comprehensive questionnaire collected information on a) basic demographics, b) medical and surgical history, c) PHQ-12 somatisation score, which was further condensed to evaluate only non-intestinal/non-musculoskeletal somatic symptoms (maximum number=10), d) short-form 8 quality of life (SF8-QOL) and e) the Rome IV diagnostic questionnaire for the presence of FGIDs. We also analysed a question stem from the Rome IV diagnostic questionnaire specifically asking about the frequency of abdominal pain over the last 3 months. Detailed information on the questionnaires is provided in **supplementary material 1**.

Statistical analysis

Statistical analysis was carried out using SPSS version 25.0 software, with significance set at a p-value of <0.05. There was no missing data because the online questionnaire required participants to complete each applicable question before being allowed to move onto the next step. Categorical variables were summarized by descriptive statistics, including total numbers and percentages, with comparisons between groups performed using the chi-square test. Continuous variables were summarized by mean and standard deviation, with difference between two independent groups performed using the unpaired student T-test.

We then performed binary logistic regression to establish the strength of associations for FGIDS and surgical interventions in subjects with HSD/hEDS compared to population controls. This was initially performed unadjusted and then adjusted for the number of non-GI/non-musculoskeletal somatic symptoms, as we deemed this to be a potentially relevant confounder.[13]

Results

Characteristics

The mean-age of the HSD/hEDS cases and the matched population controls was 39 years (SD=13), with the majority aged between 18-34 years (41%) and 35-49 years (36%). Almost all were female (96%) and over 90% were white.

Prevalence of Rome IV FGIDs

Nearly all subjects (98%, n=591/603) with HSD/hEDS fulfilled symptom-based criteria for one or more Rome IV FGIDs compared with 47% (n=285/603) of the population controls; p<0.0001. As listed in table 1, the parts of the digestive tract most commonly affected by FGIDs in HSD/hEDS and control subjects were the bowel (90% vs. 40%, respectively), gastroduodenal (70% vs. 13%), oesophageal (56% vs. 6%), and anorectal (53% vs. 9%) regions; all p<0.0001. Further, 84% of subjects with HSD/hEDS subjects had a FGID in two or more organ regions, whereas this occurred in 15% of the population controls; figure 1. The average number of afflicted FGID regions in HSD/hEDS was 2.7 versus 0.7 in population controls, p<0.0001.

With regards to individual FGID entities in HSD/hEDS and population controls, the most notable were functional dyspepsia (57% vs. 9%), irritable bowel syndrome (54% vs. 8%), functional dysphagia (42% vs. 4%), rumination (31% vs. 5%), proctalgia fugax (29% vs. 6%), functional heartburn (24.5% vs. 2%), faecal incontinence (16% vs.2%) chronic nausea and vomiting syndrome (14% vs. 1%), and opioid induced constipation (10% vs.3%); all p-value<0.0001.

Frequency of abdominal pain

Over the past 3 months, subjects with HSD/hEDS were significantly more likely than population controls to experience abdominal pain at least 1 day per week (75% vs. 14%,p<0.0001); figure 2. Most notably, subjects with HSD reported having abdominal pain 2-3 days per week (17.8% vs. 4.4% in controls), most days (23.1% vs. 2%), everyday (9.5% vs. 0.8%) and multiple times per day (17.6% vs. 0.9%).

Non-GI/non-musculoskeletal somatic symptoms and quality of life scores

Compared with population controls, subjects with HSD/hEDS reported a significantly higher PHQ-12 somatisation score (14.2 vs. 5.6 in controls), with over 95% being categorised as having medium (30% vs.

23.5%) to high (66% vs. 5.5%) somatisation severity. The number of non-GI/non-musculoskeletal somatic symptoms was also greater in HSD/hEDS compared with population controls (7.1 vs. 3.3, p<0.0001). The prevalence of individual somatic symptoms over the preceding four weeks are shown in figure 3, demonstrating that subjects with HSD/hEDS were significantly more likely than population controls to report bothersome symptoms of headache (85% vs. 58%), chest pain (60% vs. 15%), dizziness (86% vs. 24%), fainting spells (29% vs. 5%), palpitations (82% vs. 24%), breathlessness (70% vs. 26%), lethargy (99% vs. 66%), insomnia (93% vs. 57%), dyspareunia (51% vs. 8%), and menstrual cramps (52% vs. 45%); all p<0.0001. Subjects with HSD/hEDS recorded significantly lower (abnormal) scores across all physical and mental QOL domains; table 1.

Medical history and Healthcare utilisation

Subjects with HSD/hEDS were significantly more likely than population controls to have sought gastrointestinal-related consultations, in particular with their general practitioner (79% vs. 24%) and a gastroenterologist (53% vs. 7%). Approximately 20% of HSD/hEDS subjects had seen a surgeon or a gynaecologist, compared with ~1.5% of the population controls.

A significantly greater prevalence of doctor-diagnosed irritable bowel syndrome (57% vs. 16%) and reflux/dyspepsia (46% vs. 12%) was reported in HSD/hEDS compared with population controls. In addition, 40% of subjects with HSD/hEDS reported a doctor-diagnosis of fibromyalgia and 38% reported chronic fatigue syndrome.

Finally, subjects with HSD/HEDS reported significantly greater use of medication and alternative medicine supplements compared with population controls; table 1. This included the use of GI-specific medications (e.g. antacids, laxatives), analgesics (84% vs. 29%), and neuromodulators (41% vs. 20%).

They were significantly greater rates of abdominal surgery in HSD/hEDS, in terms of cholecyestectomy (11% vs. 3.5%), appendectomy (12% vs. 7%) and hysterectomy (9% vs. 5%), with a trend towards increased bowel resection (2% vs. 1%). Subjects with HSD/hEDS had one (19% vs. 12%) or more (7% vs. 2%) of the aforementioned abdominal operations, compared with controls; p<0.0001.

Comparing disease burden in HSD/hEDS subjects vs. the general population who have FGIDs

Following sub-group analysis, HSD/hEDS subjects with FGIDs (n=591) also demonstrated far greater illness burden than their general population counterparts who exhibited FGIDs (n=285); table 2. This was reflected in healthcare utilisation, quality of life, somatic symptoms, and FGIDs – where the mean number of afflicted FGID regions was 2.8 vs. 1.4, p<0.0001.

Strength of associations

The unadjusted odds ratio (UOR) for the presence of FGIDs and surgical interventions in subjects with HSD/hEDS compared with population controls are shown in table 3. In particular, these reveal strong associations for functional esophageal (UOR 19), gastroduodenal (UOR 16), bowel (UOR 13) and anorectal

disorders (UOR 12). Similar associations were seen for the individual FGID clinical entities, including those considered as painful FGIDS (e.g. functional chest pain, irritable bowel syndrome, dyspepsia) and non-painful FGIDS (e.g. belching, rumination, chronic nausea and vomiting). With regards to abdominal surgery, there was a significant association for cholecystectomy (UOR 3.6), appendectomy (UOR 1.7) and hysterectomy (UOR 1.8).

Following adjustments for amount of non-GI/non-musculoskeletal somatic symptoms, the associations for FGIDs in HSD/hEDS was drastically reduced by almost four-fold and in some instances was eliminated. This was seen for the painful and non-painful FGIDS. The associations for abdominal surgical interventions became largely non-significant.

Discussion

To our knowledge this is the first case-control study evaluating the prevalence and associations for Rome IV FGIDs in subjects with HSD/hEDS against age- and sex-matched general population-based controls. It shows that, in the sampled cohort, nearly all subjects with HSD/hEDS fulfil criteria for a FGID, and that individuals with this syndrome incur a considerable amount of somatic symptoms, health-related impairment and health care utilisation. These associations are drastically reduced when controlling for somatic symptoms, suggesting that they are a relevant confounder towards gastrointestinal illness behaviour in this patient group.

Our findings corroborate with the published literature regarding the high prevalence of FGIDs in HSD/hEDS, although previous studies have been limited to case-series, cohort studies, and small secondary care case-control studies.[2-12] Notably, two national cohort studies, comprising 134 EDS societal members from France and over 1000 EDS societal members in the United States, reported that 84% and 93% qualified for at least one FGID based on the Rome III criteria, respectively.[11,12] Our study substantially adds to the literature due to its large sample size, national dissemination, case-control design, exclusion of subjects with organic gastrointestinal pathology, evaluation of health impairment and healthcare utilisation, and the use of the newly validated Rome IV diagnostic criteria. Importantly, we also evaluated a myriad of somatic symptoms but without musculoskeletal symptom reporting, as the latter are directly related to HSD/hEDS and their inclusion in analyses of data from these individuals may inflate somatisation scores due to likely organic joint pathology involved; previous studies have not controlled for this issue.[8] Moreover, we provide data on the number of somatic sites involved, not just an overall somatisation severity score, as arguably this provides a clinically more relevant picture of disease phenotype.

The study has potential limitations. For example, it is uncertain whether our findings in HSD/hEDS societal members can be generalised to the wider HSD/hEDS community. However, we feel it will represent a vast majority, particularly those seeking gastrointestinal consultations, given the similarities in severe illness-burden shared by HSD/hEDS societal members and those attending clinical practise; data to suggest this is appropriately referenced and discussed in greater depth within **supplementary material 2**. In addition, issues pertaining to diagnostic clarity/nomenclature, as well as controversial factors speculated to contribute to FGIDs in HSD/hEDS but not studied in our dataset (e.g. connective tissue abnormalities, gut dysmotility,

autonomic dysfunction, and mast cell activation disorder) are also discussed in **supplementary material 2**, with their role largely refuted due to a current lack of evidence base.

Our study raises a number of clinically important points that warrant elaboration, particularly given that neurogastroenterology clinics are increasingly being referred or diagnosing patients with HSD/hEDS.[2,3] Nearly all subjects with HSD/hEDS fulfil criteria for a Rome IV FGID, with the majority having multiple affected FGID regions. A recent study has shown that accumulating FGIDs correlates with increasing health impairment and healthcare utilisation,[13] which typifies the illness pattern seen in HSD/hEDS cohort to a far greater extent than their general population counterparts who have FGIDs. To treat the highly burdensome intestinal and extra-intestinal health-related illnesses of HSD/hEDS would require dedicated clinical time and a multidisciplinary team approach, with our study suggesting a strong emphasis be placed on addressing the tendency to experience multiple somatic symptoms as they are a fundamental contributor towards reporting FGIDs and undergoing potentially unnecessary gastrointestinal surgical interventions.

In fact, the positive correlation between somatic symptoms and increased abdominal surgical rates is a well recognised but problematic issue, likely resulting from inaccurate pre-operative diagnosis or failing to appreciate the impact of somatic symptoms.[13] Previous studies have found that two-thirds of patients with HSD/hEDS do not reap benefit following an appendectomy suggesting that symptom reporting was due to somatisation as opposed to appendicitis.[15] Our dataset shows high surgical rates in HSD/hEDS, including almost 1-in-10 cases having undergone a hysterectomy, which could be considered a radical measure given that the patient cohort largely comprises women of a fertile age and previous studies have found that visceral hypersensitivity frequently drives pelvic pain in subjects with FGIDs.[16] Unfortunately, when subjects with somatic symptoms undergo such surgical interventions the resected specimen is generally normal and patients do not report clinical improvement.[17]

Hence, familiarity with somatic symptoms in HSD/hEDS and an alternate approach to treat them is required. This may be best achieved through targeting central sensitisation, a likely putative pathophysiological factor given the multitude of somatic symptoms that are commonly in play alongside the FGIDs and other medically unexplained symptoms (e.g. chronic fatigue syndrome and fibromyalgia). This assumption is in line with findings of elevated central sensitisation inventory scores in HSD/hEDS, which correlate positively with functional disability.[18] The notion of addressing centrally-mediated mechanisms in HSD/hEDS is further supported by studies showing that psychological distress is a confounder frequently seen in this patient cohort and largely underpins gastrointestinal illness behaviour.[19] Whilst specific markers of psychological distress were not studied in our dataset, elsewhere a recent retrospective study found that almost half of patients with HSD/hEDS have a clinical psychiatric disorder, which was significantly associated with somatic muscular pain, nerve-related pain and gastrointestinal dysfunction.[20] Moreover, triggering of central sensitisation within the dorsal horns, via persistent nociceptive input from joint abnormalities, is the postulated mechanism behind chronic non-cancer pain in HSD/hEDS.[21] Thus, in view of the data largely implicating psychosomatic disorders

and central sensitisation as being strongly associated with FGIDs in HSD/hEDS, one would advocate that a fundamental aspect of their care encompasses behavioural and pharmacological psychotherapy.[22,23] Randomised controlled trials in FGIDs -including subjects with concurrent somatisation- have shown that psychological therapies can lead to an improvement in overall symptoms, with postulated mechanisms being through central desensitisation, reduction in hypersensitivity, increase in brain-derived neurotropic factor, and an improvement in mood.[22,23] Similar studies are needed in HSD/hEDS.

Finally, it is worth highlighting the alarmingly high prevalence of pain medication use in HSD/hEDS, which is in line with global epidemic of opioid use and abuse.[24] Although our study did not specifically ask about opioid use, we did note that over 80% of subjects with HSD/hEDS were taking analgesics. A recent large retrospective evaluation of prescription medication use amongst adults with EDS noted the vast majority to be taking analgesics, of which opioids accounted for almost two-thirds.[25] On this basis, the likely assumption is that opioids are the most commonly consumed analgesic in our HSD/hEDS cohort, and when we adjusted for this within the logistic regression model it reduced the association for FGIDs *(data not shown)*, albeit to a lesser degree than somatic symptoms, suggesting that they are also key players towards ill-health and should be weaned. This would fit with ample evidence linking opioids to compounding and deleterious gastrointestinal-related adverse effects, collectively known as opioid–induced bowel dysfunction.[26] Among the most common symptoms of opioid-induced bowel dysfunction are abdominal pain, nausea, reflux, vomiting, and constipation; what can become extremely troublesome for patients and healthcare providers alike is the development of narcotic bowel syndrome, an opioid induced paradoxical hyperalgesia.[26] Opioids are also associated with substantial systemic harm such as worsening psychopathology, addiction, tolerance, and premature death.[24] This is of great concern in HSD/hEDS where rapid dose escalation of opioids, alongside the co-prescription of sedative drugs such as benzodiazepines, is commonly seen.[25] Therefore, extreme caution must be advised when prescribing opioids for chronic non-cancer pain conditions, like HSD/hEDS, as the risks are substantial yet the evidence to show benefit is lacking.[24]

In conclusion, this large case-control study shows that HSD/hEDS societal members report a very high prevalence of symptoms compatible with Rome IV FGIDs and incur considerable health impairment and health care utilisation. These gastrointestinal associations of the syndrome are drastically reduced, and in some instances eliminated, when controlling for the tendency to report multiple somatic symptoms.

Table 1: Characteristics of subjects with HSD/hEDS compared to age- and sex- matched general population controls

	General population controls (n=603)	HSD/hEDS (n= 603)	P-value
Demographics			
Female	580 (96%)	580 (96%)	1.0
Age	39 (13)	39 (13)	1.0
Age category			
18 to 34 years	248 (41%)	248 (41%)	
35 to 49 years	214 (36%)	225 (37%)	0.85
50 to 64 years	121 (20%)	110 (18%)	
65+ years	20 (3%)	20 (3%)	
White race	488/535 (91%)	566 (94%)	0.1
Single relationship status	264 (44%))	260 (43%)	0.86
Symptom Scores			
Somatic Symptom Reporting			
PHQ-12 somatisation score	5.6 (3.8)	14.2 (3.9)	<0.0001
PHQ-12 severity category			
Mild (PHQ ≤3)	199 (33%)	1 (0.2%)	
Low (PHQ 4-7)	228 (38%)	24 (4%)	<0.0001
Medium (PHQ 8-12)	142 (23.5%)	180 (30%)	
High (PHQ ≥13)	34 (5.5%)	398 (66%)	
Number of non-GI somatic symptoms (max =12)	4.4 (2.6)	9.0 (1.9)	<0.0001
Number of non-GI/non-musculoskeletal somatic symptoms (max=10)	3.3 (2.1)	7.1 (1.8)	<0.0001
Short-Form 8 quality of life			
Physical Functioning	48.2 (8.5)	33.3 (8.3)	<0.0001
Role Physical	48.5 (8.9)	31.2 (8.3)	<0.0001
Bodily Pain	50.6 (9.5)	34.7 (6.6)	<0.0001
General Health	45.6 (7.8)	35.2 (7.0)	<0.0001
Vitality	46.9 (8.7)	38.5 (6.5)	<0.0001
Social Functioning	47.8 (9.5)	34.9 (8.6)	<0.0001
Role Emotional	47.1 (7.8)	40.2 (9.5)	<0.0001
Mental Health	46.4 (10.7)	38.7 (11.3)	<0.0001
Functional gastrointestinal disorders			
Functional Oesophageal Disorders	38 (6%)	338 (56%)	<0.0001
Functional Chest pain	6 (1%)	78 (13%)	<0.0001
Functional Heartburn	10 (2%)	148 (24.5%)	<0.0001
Globus	3 (0.5%)	11 (1.8%)	0.13
Functional dysphagia	26 (4%)	253 (42%)	<0.0001
Functional Biliary Disorders	2 (0.3%)	7 (1.2%)	0.18
Functional Gastroduodenal Disorders	77 (13%)	423 (70%)	<0.0001

Functional dyspepsia	54 (9%)	341 (57%)	<0.0001
Postprandial distress syndrome	46 (8%)	299 (50%)	<0.0001
Epigastric pain syndrome	18 (3%)	197 (33%)	<0.0001
Belching	10 (2%)	70 (12%)	<0.0001
Rumination	28 (5%)	187 (31%)	<0.0001
Chronic Nausea and Vomiting Syndrome	6 (1%)	86 (14%)	<0.0001
Cyclical Vomiting Syndrome	7 (1%)	64 (11%)	<0.0001
Functional Bowel Disorders	242 (40%)	541 (90%)	<0.0001
Irritable Bowel Syndrome	48 (8%)	326 (54%)	<0.0001
Functional constipation	59 (10%)	75 (12%)	0.14
Opioid induced constipation	18 (3%)	60 (10%)	<0.0001
Functional diarrhoea	28 (4.6%)	31 (5%)	0.69
Functional bloating and distension	39 (6.5%)	17 (2.8%)	0.003
Unspecified functional bowel disorder	57 (9.5%)	60 (10%)	0.77
Centrally Mediated Abdominal Pain Syndrome	0 (0%)	3 (0.5%)	0.25
Functional Anorectal Disorders	53 (9%)	318 (53%)	<0.0001
Faecal incontinence	12 (2%)	99 (16%)	<0.0001
Levator Ani Syndrome	7 (1%)	113 (19%)	<0.0001
Proctalgia Fugax	37 (6%)	175 (29%)	<0.0001
Healthcare utilisation			
Gastrointestinal-related consultations			
Seen General Practitioner	143 (24%)	476 (79%)	<0.0001
Seen Gastroenterologist	42 (7%)	322 (53%)	<0.0001
Seen Gynaecologist	9 (1.5%)	125 (21%)	<0.0001
Seen Surgeon	7 (1.2%)	118 (20%)	<0.0001
Medication			
Laxatives	30 (5%)	167 (28%)	<0.0001
Anti-diarhoeals	17 (3%)	47 (8%)	<0.0001
Antiemetic	13 (2%)	147 (24%)	<0.0001
Antacids	102 (17%)	322 (53%)	<0.0001
Antispasmodics	24 (4%)	125 (21%)	<0.0001
Herbal remedies	30 (5%)	144 (24%)	<0.0001
Traditional Chinese Medicine	1 (0.2%)	8 (1.3%)	0.04
Analgesia	173 (29%)	507 (84%)	<0.0001
Neuromodulators	120 (20%)	249 (41%)	<0.0001
Abdominal Surgery			
Cholecystectomy	21 (3.5%)	69 (11%)	<0.0001
Appendectomy	44 (7%)	71 (12%)	0.01
Hysterectomy	31 (5%)	53 (9%)	0.01
Bowel resection	5 (1%)	12 (2%)	0.09

Note: Data are presented as mean (SD) or n (%)

Table 2: Characteristics of subjects with HSD/hEDS who have FGIDs (n=591) and those of the general population who have FGIDs (n=285)

	General population controls with FGIDs (n=285)	HSD/hEDS with FGIDs (n=591)	P-value
Demographics			
Female	278 (98%)	569 (96%)	0.35
Age	39 (12.8)	39 (12.9)	0.99
White race	228 (91%)	555 (94%)	0.16
Single	125 (44%)	257 (44%)	0.92
Symptom Scores			
Somatic Symptom Reporting			
PHQ-12 somatisation score	7.4 (3.9)	14.3 (3.8)	<0.0001
PHQ-12 severity category			
Mild (PHQ ≤3)	48 (17%)	0 (0%)	<0.0001
Low (PHQ 4-7)	104 (37%)	22 (4%)	
Medium (PHQ 8-12)	101 (35%)	173 (29%)	
High (PHQ ≥13)	32 (11%)	396 (67%)	
Number of non-GI somatic symptoms (max=12)	5.6 (2.4)	9.1 (1.9)	<0.0001
Number of non-GI/non-musculoskeletal somatic symptoms (max=10)	4.2 (2.1)	7.1 (1.8)	<0.0001
Short-Form 8 quality of life			
Physical Functioning	45.7 (9.8)	33.0 (8.2)	<0.0001
Role Physical	45.7 (10.2)	31.0 (8.2)	<0.0001
Bodily Pain	46.5 (9.3)	34.7 (6.5)	<0.0001
General Health	42.8 (8.1)	35.2 (6.9)	<0.0001
Vitality	44.1 (8.6)	38.4 (6.4)	<0.0001
Social Functioning	44.7 (10.5)	34.9 (8.5)	<0.0001
Role Emotional	45.0 (9.1)	40.2 (9.5)	<0.0001
Mental Health	43.2 (11.3)	38.7 (11.3)	<0.0001
Functional gastrointestinal disorders			
Functional Oesophageal Disorders	38 (13%)	338 (57%)	<0.0001
Functional Chest pain	6 (2%)	78 (13%)	<0.0001
Functional Heartburn	10 (3.5%)	148 (25%)	<0.0001
Globus	3 (1%)	11 (2%)	0.37
Functional dysphagia	26 (9%)	253 (43%)	<0.0001
Functional Biliary Disorders	2 (0.7%)	7 (1.2%)	0.4
Functional Gastroduodenal Disorders	77 (27%)	423 (72%)	<0.0001
Functional dyspepsia	54 (19%)	341 (58%)	<0.0001
Postprandial distress syndrome	46 (16%)	299 (51%)	<0.0001
Epigastric pain syndrome	18 (6%)	197 (33%)	<0.0001
Belching	10 (3.5%)	70 (12%)	<0.0001
Rumination	28 (10%)	187 (32%)	<0.0001

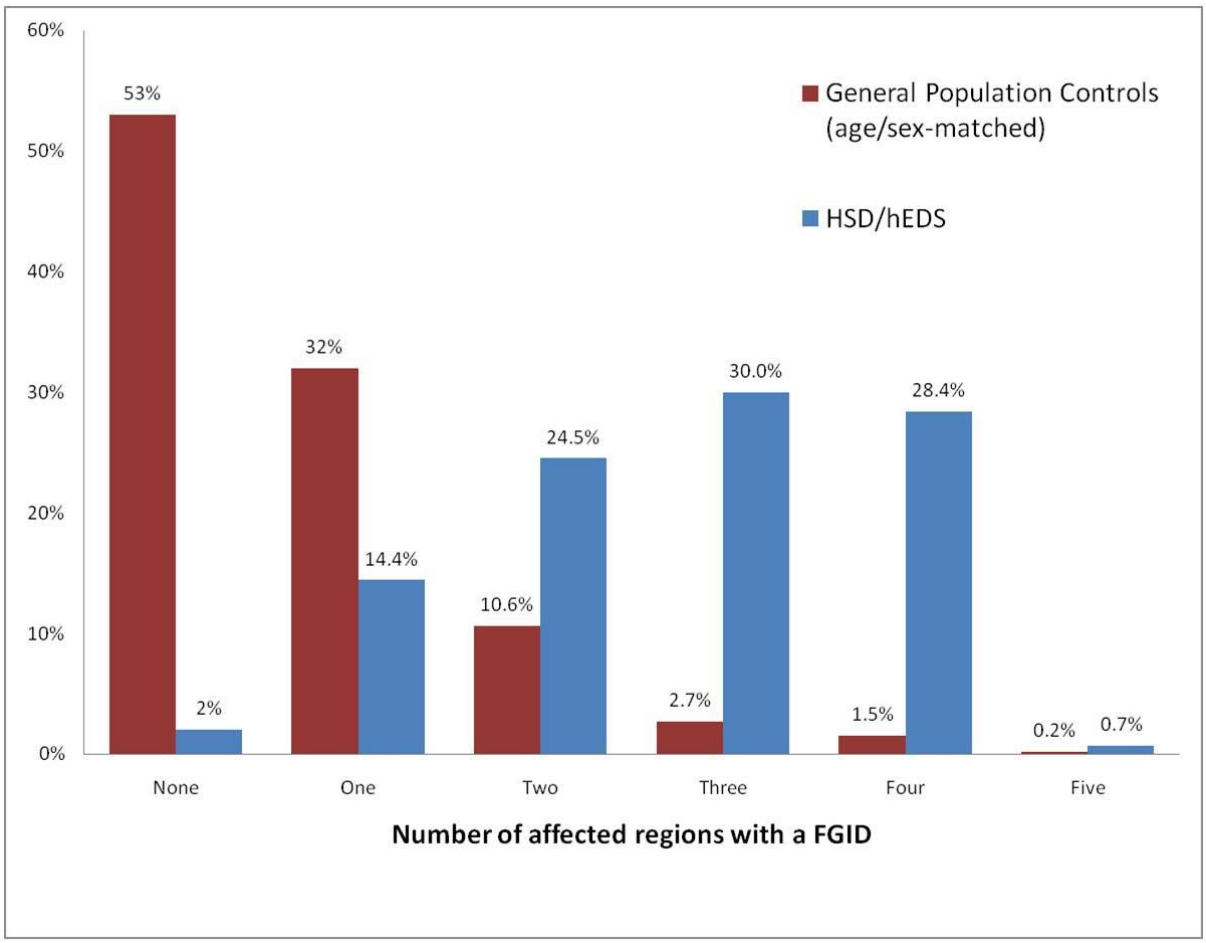
Chronic Nausea and Vomiting Syndrome	6 (2%)	86 (15%)	<0.0001
Cyclical Vomiting Syndrome	7 (2.5%)	64 (11%)	<0.0001
Functional Bowel Disorders	242 (85%)	541 (92%)	0.003
Irritable Bowel Syndrome	48 (17%)	326 (55%)	<0.0001
Functional constipation	59 (21%)	75 (13%)	0.002
Opioid induced constipation	18 (6%)	60 (10%)	0.06
Functional diarrhoea	28 (10%)	31 (5%)	0.01
Functional bloating and distension	39 (14%)	17 (3%)	<0.0001
Unspecified functional bowel disorder	57 (20%)	60 (10%)	<0.0001
Centrally Mediated Abdominal Pain Syndrome	0 (0%)	3 (0.5%)	0.31
Functional Anorectal Disorders	53 (19%)	318 (54%)	<0.0001
Faecal incontinence	12 (4%)	99 (17%)	<0.0001
Levator Ani Syndrome	7 (2.5%)	113 (19%)	<0.0001
Proctalgia Fugax	37 (13%)	175 (30%)	<0.0001
Healthcare utilisation			
Gastrointestinal-related consultations			
Seen General Practitioner	107 (38%)	471 (80%)	<0.0001
Seen Gastroenterologist	35 (12%)	321 (54%)	<0.0001
Seen Gynaecologist	9 (3%)	124 (21%)	<0.0001
Seen Surgeon	7 (2.5%)	117 (20%)	<0.0001
Medication			
Laxatives	28 (10%)	167 (28%)	<0.0001
Anti-diarhoeals	15 (5%)	47 (8%)	0.15
Antiemetic	12 (4%)	146 (25%)	<0.0001
Antacids	68 (24%)	320 (54%)	<0.0001
Antispasmodics	19 (7%)	125 (21%)	<0.0001
Herbal remedies	19 (7%)	139 (24%)	<0.0001
Traditional Chinese Medicine	1 (0.4%)	8 (1.4%)	0.17
Analgesia	119 (42%)	499 (84%)	<0.0001
Neuromodulators	82 (29%)	245 (42%)	<0.0001
Abdominal Surgery			
Cholecystectomy	13 (5%)	69 (12%)	0.001
Appendectomy	25 (9%)	70 (12%)	0.17
Hysterectomy	24 (8%)	52 (9%)	0.85
Bowel resection	5 (2%)	12 (2%)	0.8

Note: Data are presented as mean (SD) or n (%)

Table 3: Odds ratio (OR) for functional gastrointestinal disorders and abdominal surgery in subjects with HSD/HEDS compared to age- and sex- matched general population controls

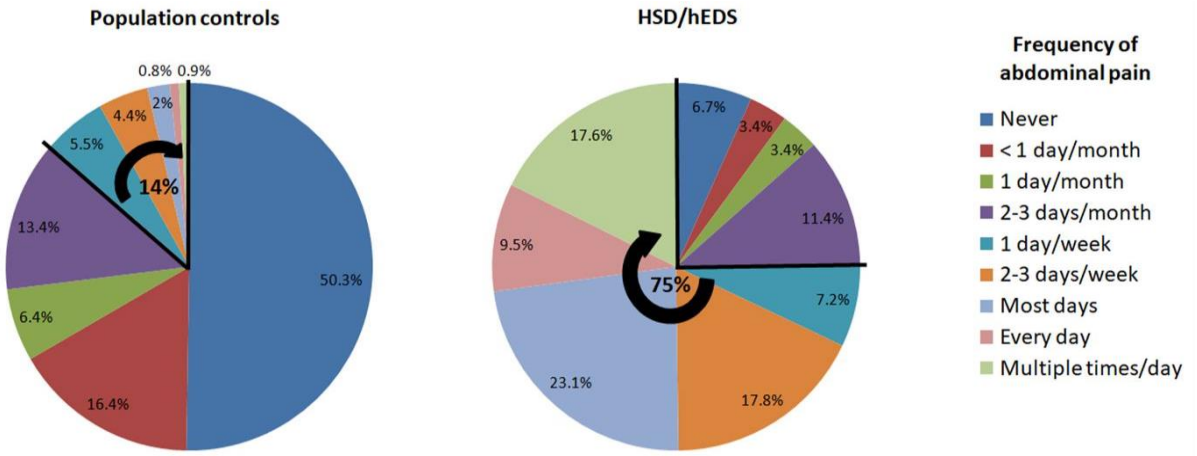
	Unadjusted OR	Adjusted OR (controlling for number of non-GI/non-musculoskeletal somatic symptoms)
Functional Gastrointestinal Disorders		
Functional Oesophageal disorders	19.0 (13.2-27.3)	6.1 (4.0-9.2)
Functional chest pain	14.8 (6.4-34.2)	7.4 (2.9-19.0)
Functional heartburn	19.3 (10.1-37.0)	5.5 (2.7-11.3)
Functional dysphagia	16.0 (10.5-24.5)	4.9 (3.0-8.0)
Functional Gastroduodenal Disorders	16.1 (11.9-21.6)	5.1 (3.6-7.3)
Functional dyspepsia	13.2 (9.6-18.3)	3.9 (2.7-5.7)
Postprandial distress syndrome	11.9 (8.5-16.7)	3.6 (2.4-5.3)
Epigastric pain syndrome	15.8 (9.6-26.0)	3.8 (2.2-6.7)
Belching	7.8 (4.0-15.3)	2.6 (1.2-5.7)
Rumination	9.2 (6.1-14.0)	4.1 (2.5.6.8)
Chronic nausea & vomiting syndrome	16.6 (7.2-38.2)	4.2 (1.7-10.5)
Cyclic vomiting syndrome	10.1 (4.6-22.3)	2.3 (0.95-5.6)
Functional Bowel Disorder	13.0 (9.6-17.7)	4.3 (3.0-6.3)
Irritable bowel syndrome	13.6 (9.7-19.0)	4.6 (3.1-6.9)
Opioid induced constipation	3.6 (2.1-6.2)	1.6 (0.8-3.2)
Functional Anorectal disorders	11.6 (8.4-16.0)	4.6 (3.1-6.8)
Faecal incontinence	9.7 (5.3-17.8)	3.7 (1.8-7.6)
Levator Ani syndrome	19.6 (9.1-42.5)	7.9 (3.4-18.4)
Proctalgia fugax	6.3 (4.3-9.1)	3.0 (1.9-4.7)
Abdominal Surgery		
Cholecystectomy	3.6 (2.2-5.9)	2.8 (1.5-5.5)
Appendectomy	1.7 (1.1-2.5)	1.5 (0.86-2.5)
Hysterectomy	1.8 (1.1-2.8)	1.7 (0.9-3.2)

Figure 1: Number of regions affected with a functional gastrointestinal disorder (FGID) is subjects with HSD/HEDS compared with the general population



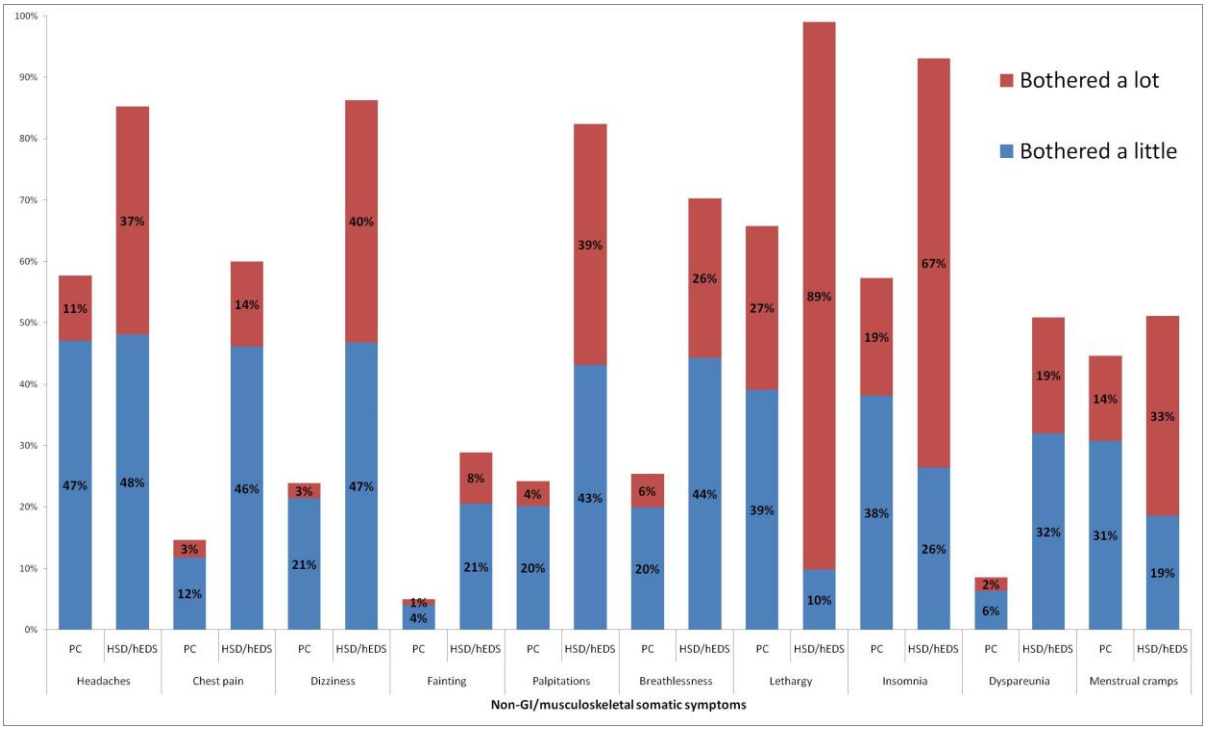
Note: 98% of subjects with HSD/hEDS fulfilled symptom based criteria for a Rome IV FGID, with the majority (84%) reporting ≥ 2 affected regions. In contrast, 47% of age/sex-matched general population controls have a FGID, which is limited to either one (32%) or two (10.6%) regions.

Figure 2: Frequency of abdominal pain in the last 3 months between subjects with HSD/hEDS and population controls



As denoted by the arrows, subjects with HSD/HEDS were significantly more likely to have abdominal pain at least 1 day per week compared with population controls (75% vs. 14%, $p<0.0001$).

Figure 3: Presence of bothersome non-GI/non-musculoskeletal somatic symptoms over the past four weeks in subjects with HSD/hEDS and population controls (PC)



Subjects with HSD/hEDS were significantly more likely than population controls to experience bothersome somatic symptoms; $p<0.0001$ for each symptom domain

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Supplementary Material 1

Methods section - Questionnaire

a) Medical history/healthcare utilisation - Subjects were asked whether they had consulted any of the following specialists for gastrointestinal symptoms: general practitioner, gastroenterologist, gynaecologist, and surgeon. A reported doctor-diagnosis of irritable bowel syndrome and reflux/dyspepsia was determined, but data for chronic fatigue syndrome and fibromyalgia was only available for the HSD/hEDS group (where a high prevalence has previously been observed).[1-3] We also enquired whether the following medications were being taken on at least a weekly basis: laxatives, anti-diarrheals, antiemetics, antacids, antispasmodics, herbal remedies, traditional Chinese medicine, analgesics, and neuromodulators. Finally, they were asked about history of abdominal surgeries, that is cholecystectomy, appendectomy, hysterectomy, and bowel resection.

b) Patient health questionnaire (PHQ)-12 non GI somatic scale[4,5] - The PHQ-12 is a modified version of the widely used PHQ-15 somatisation questionnaire that excludes the three GI symptoms (nausea, abdominal pain, altered bowel habit), as these are likely to be directly related to FGIDs. As a result, the PHQ-12 only records bothersome non-GI symptoms over the past month. The twelve symptoms assessed are back pain, limb pain, headaches, chest pain, dizziness, fainting spells, palpitations, breathlessness, menstrual cramps, dyspareunia, insomnia, and lethargy. Subjects were asked to rate how much they had been troubled by these 12 symptoms over the last four weeks as 0 ("not bothered at all"), 1 ("bothered a little"), or 2 ("bothered a lot"). The PHQ-12 responses can be used to calculate a) the number of sites reporting somatic symptoms (ranging from 0 to 12), b) the overall somatisation severity score (ranging from 0 to 24), and c) the somatisation severity category (mild, PHQ ≤3; low, PHQ 4-7; medium, PHQ 8-12; high, PHQ ≥13). However, given that the PHQ-12 somatisation scale includes back pain and limb pain, which in HSD/hEDS may arguably be due to an organic disease process, we also present data on the number of somatic symptoms having excluded these two musculoskeletal symptoms; this provides a maximum number of 10 non-GI/non-musculoskeletal somatic symptoms. Higher scores represent greater somatisation, which is generally considered to reflect a psychological tendency to report and experience a high amount of general body symptoms.

c) Short form (SF)-8 Health Survey[6] - This validated questionnaire is commonly used in large scale epidemiological studies to assess general health related quality of life (QOL) over the past month. The 8 items enquire about physical functioning, physical role, bodily pain, general health perceptions, vitality, social functioning, emotional role, and mental health. The scores are normalised to the general population that has a mean score of 50.[6] A high score represents better QOL, whereas low scores represent poorer QOL.

d) Rome IV diagnostic questionnaire[7] – This validated questionnaire is benchmarked as the principal diagnostic tool for FGIDs, and used for diagnosing individuals with these disorders for inclusion into clinical trials and in epidemiological surveys. For the purpose of this study we report individuals meeting criteria for FGIDs and then categorise them into one of the six anatomical GI regions that they belong to i.e. esophageal, gastroduodenal, gallbladder, bowel, anorectal, and centrally-mediated disorders of GI pain. Finally, we separately analysed a question stem from the Rome IV diagnostic questionnaire that specifically asks about the frequency of abdominal pain over the last 3 months, with nine answers that range from "never having abdominal pain" to experiencing "abdominal pain multiple times per day".

Supplementary Material 2

Discussion – Potential limitations, diagnostic accuracy, and generalizability of findings

There are potential limitations to our study. Firstly, it could be argued that the high prevalence of FGIDs in HSD/hEDS may be accounted for by connective tissue abnormalities within the gastrointestinal tract, which was not possible to explore in our study. However, to date, neither collagen defects nor associated mutations have been found within the GI tract of patients with HSD/hEDS.[8] Moreover, any potential association with disordered gut motility has shown conflicting results, with data being limited to a few case series or non-matched case-control studies, and without controlling for common confounders of GI transit (e.g. opiates, tricyclic antidepressants).[2,9,10] A relationship between autonomic dysfunction and mast cell activation syndrome disorders has also been observed in HSD/hEDS and suggested to cause or aggravate some of the symptoms reported.[11,12] However, these poorly understood concepts are under scrutiny, as a direct pathophysiological basis to explain their presence in HSD/hEDS has not yet been established.[13] Rather, the presence of autonomic dysfunction has been suggested to arise as a secondary epiphenomenon due to a combination of confounding factors including somatic hypervigilance, psychological distress, physical de-conditioning, poor oral intake, and the use of drugs that can affect neuronal function and possess vasoactive properties (e.g. opiates).[12,13] With regards to mast cell activation syndrome, a recent comprehensive literature review questioned its diagnosis being made outside the realms of allergy units and suggested any current association with HSD/hEDS as controversial.[13] In summary, more robust research and evidence-base for the aforementioned potential factors is warranted.

Secondly, we did not have access to medical records to confirm or refute the declared doctor diagnosis of HSD/hEDS, although arguably this can resemble clinical practise whereby a gastroenterologist or surgeon will not have the expertise to question or disentangle the presumed underlying rheumatological diagnosis but rather be focused on evaluating the troublesome gut symptoms. Indeed, even within specialist rheumatology clinics issues with nomenclature have been inherent within the field of hypermobility-related disorders, thereby leading to a heterogeneous pool of patients commonly referred to as HSD/hEDS. The reasons for diagnostic blurring have historically been attributed to the subjective application of overlapping criteria for

HSD and hEDS, compounded by the absence of an objective biomarker. To overcome these issues, an international consortium published updated guidelines in 2017, whereby far more stringent criteria will hopefully improve the diagnostic specificity of hEDS and allow clear distinction from HSD.[14,15] In fact, subsequent application of the change in criteria has found that of almost 300 patients previously diagnosed with hEDS none fulfilled the new diagnostic criteria for hEDS; instead they were all re-classified as HSD.[16] This would suggest that under the new classification criteria our findings are mainly applicable to patients with HSD as opposed to the rare hEDS; however, conceivably patients may still present under the umbrella term for both and gastroenterologists should strive to obtain diagnostic clarity from rheumatologists. Our study should also not be extrapolated to the other EDS subtypes, such as vascular EDS, which have recognised and potentially catastrophic gastrointestinal complications.[14]

Finally, there are issues of selection bias when conducting surveys, irrespective of where they are performed (e.g. population-based, primary or secondary-care, societal groups) or the methodology used to collect data (e.g. postal, telephone, or online). Our study sampled a fifth of the online HSD/hEDS society cohort which may viewed as not reflective of non-responders or non-societal members. Nevertheless, it is the largest study of this nature to date and did capture individuals throughout the UK, as opposed to within the confines of a single centre. We also attempted to reduce potential bias by promoting our survey as “general health” and not “gastroenterology-related”. In addition, quality assurance measures were built in within the online questionnaire system to ensure we had no missing data and could also exclude inconsistent responders, the latter by attention check and repeat questions. It must also be borne in mind that the HSD/hEDS societal sample comprised of mainly young to middle aged female subjects who were heavily debilitated by widespread symptoms; this demographic profile is characteristic of the HSD/hEDS patient case load seen within clinical practise,[1,2,8,17-24] of which the majority (~60%) cluster into a complex/severe phenotypic group comprising highly burdensome intestinal and extra-intestinal complaints.[25,26] Hence, although our findings may not necessarily be generalizable to the wider HSD/hEDS community, they are likely to represent a substantial proportion and of those seeking GI consults. Another issue worth clarifying is the almost 50% prevalence of FGIDs seen in the population control group which - at first glance - may be viewed as on the higher side but does fit with the literature given that a third of adults across all age groups (spanning from 18 to over 65 years) collectively fulfil criteria for any FGID,[27] with the highest concentration of afflicted subjects being young to middle aged women.[28]

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