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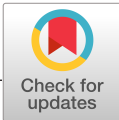
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# Functional gastrointestinal disorders are increased in joint hypermobility-related disorders with concomitant postural orthostatic tachycardia syndrome

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## Abstract

**Background:** Individuals with hypermobility spectrum disorders/hypermobile Ehlers-Danlos syndrome (HSD/hEDS) frequently fulfill criteria for Rome IV functional gastrointestinal disorders (FGIDs). Postural orthostatic tachycardia syndrome (POTS) is also commonly reported in HSD/hEDS and may impact on co-morbidity with and severity of FGIDs, although this remains to be studied. We determined the impact of concomitant POTS and HSD/hEDS on their association with Rome IV FGIDs.

**Methods:** With the help of the charity organization Ehlers-Danlos Support UK, an online cross-sectional health survey was completed by individuals with HSD/hEDS. The survey enquired for (a) self-reported doctor diagnosis of POTS, chronic fatigue syndrome, and fibromyalgia, (b) the presence and symptom frequency of Rome IV FGIDs, and (c) anxiety and depression scores.

**Key Results:** Of 616 subjects with HSD/hEDS, 37.5% reported a doctor diagnosis of POTS. POTS-positive individuals were significantly younger than POTS-negative subjects (37 vs 40 years,  $P = 0.002$ ), more likely to report chronic fatigue syndrome (44% vs 31%,  $P < 0.0001$ ), and showed a trend toward increased prevalence of fibromyalgia (44% vs 37%,  $P = 0.06$ ) and higher depression score ( $P = 0.07$ ). POTS-positive subjects were also more likely to fulfill criteria for Rome IV FGIDs across various organ domains and experienced both upper and lower gastrointestinal symptoms significantly more frequently. The increased associations for FGIDs and GI symptom frequency remained unchanged in HSD/hEDS subjects with POTS following adjustments for age, chronic fatigue syndrome, fibromyalgia, and depression scores.

**Conclusions and Inferences:** The high FGID burden in HSD/hEDS is further amplified in the presence of POTS. Future studies should elucidate the mechanism by which POTS arises in HSD/hEDS and is associated with increased GI symptoms.

## KEYWORDS

functional gastrointestinal disorders, joint hypermobility, postural orthostatic tachycardia syndrome

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## 1 | INTRODUCTION

Hypermobile spectrum disorders (HSD) affect approximately 3% of the population and are defined as musculoskeletal symptoms in an individual with joint hypermobility but without systemic manifestations.<sup>1,2</sup> Such individuals are similar to patients with Hypermobile Ehlers-Danlos Syndrome (hEDS), a rare inherited systemic connective tissue disorder affecting 1 in 5000 people. With diagnosis based entirely on clinical evaluation, HSD and hEDS have historically been merged as indistinct conditions by patients and research groups, although recent data suggest that under the new classification system the vast proportion of subjects with HSD/hEDS are represented by HSD.<sup>3</sup> The majority of subjects with HSD/hEDS are young-to-middle aged women,<sup>1,2</sup> in whom co-morbidity commonly stems from gastrointestinal complaints, which are most often attributable to functional gastrointestinal disorders (FGIDs).<sup>4</sup> Between 60% to over 90% of individuals with HSD/hEDS fulfill criteria for a Rome IV FGID,<sup>4,5</sup> with widespread somatic symptom reporting and opiate use being important mediating factors for gut symptoms.<sup>4</sup>

Postural orthostatic tachycardia syndrome (POTS) is a poorly understood condition that also predominantly affects young- to middle-aged women, between the ages of 15–45 years, and has a population prevalence of 0.2%–1%.<sup>6,7</sup> POTS is characterized by an excessive rise in heart rate of more than 30 beats per minute, without associated hypotension, that occurs within 10 minutes of standing and settles with recumbency.<sup>6,7</sup> Symptoms associated with orthostatic intolerance include pre-syncope, blurred vision, breathlessness, palpitations, chest pain, and paresthesia.<sup>6,7</sup> Moreover, a wide array of upper and lower gastrointestinal symptoms—such as dysphagia, reflux, nausea, abdominal pain, bloating, and altered bowel habit—are reported by up to 80% of subjects with POTS.<sup>8,9</sup> The etiology of gastrointestinal symptoms in POTS is not entirely clear.<sup>9,10</sup> The role of abnormal splanchnic blood flow has been questioned due to limited and conflicting results.<sup>10</sup> A prevailing hypothesis is autonomic dysfunction of the GI tract,<sup>11</sup> a concept supported by case-control studies demonstrating abnormal gastric myoelectrical activity in POTS compared with controls,<sup>12,13</sup> and gastrointestinal symptoms being more prevalent in POTS patients with autonomic neuropathy than in those without autonomic neuropathy.<sup>14</sup> However, there are also data showing that between one-third and two-thirds of POTS patients with gastrointestinal symptoms have gastric emptying rates within the normal range,<sup>9</sup> which casts doubt on autonomic dysautonomia being solely responsible.<sup>9,10</sup> Moreover, a substantial proportion of subjects with POTS have GI symptoms irrespective of posture.<sup>8,10</sup> Hence, other pathophysiological factors may be of relevance, including psychological distress, central sensitisation, and behavioral amplification which—independently associated with FGIDs—are frequently observed in POTS.<sup>8,10</sup> In summary, GI symptoms seem to be common in POTS, with the etiology being unclear but potentially multi-factorial.<sup>9,10</sup>

Of late, there has been growing interest in outlining a relationship between HSD/hEDS and POTS, although a biologically plausible mechanism to directly interlink these conditions remains elusive.<sup>15</sup> Between 60 and 80 percent of patients with HSD/

### Key Points

- In this large cohort of subjects with HSD/hEDS, over a third reported a doctor diagnosis of POTS.
- The high functional gastrointestinal disorder burden in HSD/hEDS is further amplified in those with concomitant POTS.
- How POTS arises in HSD/hEDS, and is associated with increased GI symptoms, requires elucidation in future research.

hEDS have a disorder of orthostatic intolerance, such as POTS.<sup>9</sup> Conversely, up to a fifth of patients with POTS have HSD/hEDS.<sup>16</sup> A few studies have noted increased symptom burden in individuals with comorbid HSD/hEDS and POTS, as opposed to either one alone.<sup>17,18</sup> However, these studies are small and those pertinent to gastroenterology limited to evaluating esophageal symptoms of dysphagia and reflux only.<sup>17</sup> There have been no studies examining how POTS in HSD/hEDS affects the whole repertoire of Rome IV FGIDs, in terms of their individual presence, but also symptom severity. We aimed to study this in depth by using a large sample of individuals with HSD/hEDS.

## 2 | METHODS

### 2.1 | Ethics

The study was deemed IRB-exempt by the University of Sheffield (UK) as all study participants were anonymous to the investigators.

### 2.2 | Study design and participants

In October 2018, an online health questionnaire from our research group was sent out by the charity organization Ehlers-Danlos Support UK to its 3874 contactable members. Following an e-mail reminder at 2 weeks, the survey was closed at 1 month. In total, 777 subjects with a medical diagnosis of EDS completed the survey, giving a response rate of 20%. Of these, 665 had a diagnosis of hEDS, which was subsequently re-classified as HSD/hEDS given that the society allows its members to use the terms hEDS and HSD interchangeably. Following exclusion of 49 HSD/hEDS subjects known to also have organic GI disease (28 celiac disease, 22 inflammatory bowel disease, 2 gastrointestinal cancers) this left 616 subjects with HSD/hEDS eligible for analysis.

### 2.3 | Questionnaire

The comprehensive questionnaire collected information on the following:

1. Medical history—this included basic demographic data in addition to asking HSD/hEDS subjects if they had been given a doctor diagnosis of POTS, chronic fatigue syndrome, and fibromyalgia. Subjects were also asked whether they were taking analgesics and neuromodulators, given that pain and psychological distress is commonly associated with HSD/hEDS.<sup>3,19</sup>
2. Patient health questionnaire (PHQ)-9 and General anxiety disorder (GAD)-7 questionnaire—These are nine- and seven-item questionnaires, respectively, which are widely used and validated to assess severity of symptoms of depression and generalized anxiety.<sup>20,21</sup> The PHQ-9 categorizes symptoms of depression as none (score: 0-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27).<sup>20</sup> The GAD-7 categorizes symptoms of anxiety as mild (score 0-5), moderate (6-10), moderately severe (11-15), and severe (16-21).<sup>21</sup>
3. Rome IV diagnostic questionnaire—This is a validated questionnaire benchmarked as the primary diagnostic tool for FGIDs and used to diagnose FGID for inclusion into clinical trials and observational studies.<sup>22</sup> We used the Rome IV diagnostic questionnaire to report individuals, which met the criteria of FGID in this study, and subcategorized them into one of the six anatomical GI regions in which their symptoms belong to, that is, esophageal, gastroduodenal, gallbladder, bowel, anorectal, and centrally mediated disorders of pain. We also documented what proportion of subjects reported upper and lower GI symptoms at least 1 day/week.

## 2.4 | Statistical analysis

Statistical analysis was carried out using SPSS version 25.0 software, with significance set at a *P*-value of < 0.05. There were 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 assessed using the two-group Student's *t* test.

We then performed binary logistic regression to establish the strength of associations for FGIDs in HSD/hEDS subjects with POTS compared to those without POTS. This was initially performed unadjusted and then adjusted for general health factors that were significant on univariate analysis.

## 3 | RESULTS

### 3.1 | General characteristics of HSD/hEDS subjects

The 616 included subjects with HSD/hEDS were predominantly female (93%) and of white race (94%) and had a mean age of 39 years. Nearly, all individuals with HSD/hEDS (98%) had an

FGID according to Rome IV diagnostic criteria, with the most commonly afflicted organ domains being the bowel (90%), gastroduodenal (70%), esophageal (56%), and anorectal (53%) regions. The vast majority (84%) had more than one affected GI organ region, and this has been described in more detail in a recent publication using the same population cohort.<sup>4</sup> The mean PHQ-9 and GAD-7 score among individuals with HSD/hEDS were 14.1 and 9.6, suggestive of moderate levels of depression and generalized anxiety, respectively.

### 3.2 | Comparison between HSD/hEDS subjects with and without POTS

A doctor diagnosis of POTS was reported by 37.5% (*n* = 231) of individuals with HSD/hEDS, with the remaining 62.5% (*n* = 385) not having POTS; Table 1. Those HSD/hEDS individuals classified as POTS-positive were significantly younger than POTS-negative subjects (37 vs 40 years, *P* = 0.002), more likely to report chronic fatigue syndrome (44% vs 31%, *P* < 0.0001), and showed a trend toward increased prevalence of fibromyalgia (44% vs 37%, *P* = 0.06) and higher depression symptom scores (*P* = 0.07). However, there was no statistical difference in the use of analgesia (83% vs 85%, *P* = 0.5) or neuromodulators (38% vs 44%, *P* = 0.2) between the groups.

The overall prevalence of any FGID did not differ in HSD/hEDS subjects with and without concomitant POTS (99% vs 97%, *P* = 0.13). The majority of subjects in both groups reported FGIDs from more than one organ region, although this was noted to be more common in the POTS-positive than POTS-negative cohort (88% vs 81%, *P* = 0.02). Moreover, the mean number of afflicted FGID regions in POTS-positive cohort was 2.9 compared with 2.6 in the POTS-negative group, *P* < 0.0001.

With regard to the presence of individual FGID, HSD/hEDS subjects with POTS were more likely than their POTS-negative counterparts to have (a) functional gastroduodenal disorders (75% vs 67%, *P* = 0.04), manifesting most frequently as functional dyspepsia (67% vs 50%, *P* < 0.001) and chronic nausea and vomiting syndrome (22% vs 10%, *P* < 0.001); (b) functional esophageal disorders (66% vs 50%, *P* < 0.001), manifesting most frequently as functional heartburn (31% vs 21%, *P* = 0.007) and dysphagia (51% vs 31%, *P* = 0.001); and (c) functional anorectal disorders (60% vs 49%, *P* = 0.01), manifesting most frequently as fecal incontinence (21% vs 14%, *P* = 0.02) and levator ani syndrome (24% vs 15%, *P* = 0.005). However, there was no difference between the groups with regard to the most commonly afflicted FGID region that being functional bowel disorders which was reported by 89% and 91% of subjects with and without POTS, respectively. However, within the bowel domain, there was a trend toward more irritable bowel syndrome in the POTS-positive group (59% vs 51%, *P* = 0.06).

Moreover, experiencing upper and lower gastrointestinal symptoms at least 1 day/week was significantly more common in HSD/hEDS subjects with than without concomitant POTS. This includes both painful and non-painful symptoms (Figure 1).

**TABLE 1** Characteristics of subjects with HSD/hEDS, and in those with and without concomitant POTS

	Combined (n = 616)	POTS positive (n = 231; 37.5%)	POTS negative (n = 385; 62.5%)	P-value
<b>Demographics</b>				
Female	593 (96%)	225 (97%)	368 (96%)	.3
Age	39.1 (12.8)	37 (13)	40.3 (12.6)	.002
<b>Age category</b>				
18-34 years	248 (40%)	113 (49%)	135 (35%)	.003
35-49 years	238 (39%)	78 (34%)	160 (42%)	
50-64 years	110 (18%)	31 (13%)	79 (20%)	
65 years +	20 (3%)	9 (4%)	11 (3%)	
White ethnicity	579 (94%)	216 (94%)	363 (94%)	.7
<b>General health</b>				
<b>Depression and anxiety</b>				
PHQ – 9 depression score	14.1 (6.4)	14.7 (6.5)	13.8 (6.4)	.07
GAD – 7 anxiety score	9.6 (6.4)	9.7 (6.2)	9.6 (6)	.9
Fibromyalgia	243 (39%)	102 (44%)	141 (37%)	.06
Chronic fatigue syndrome	235 (38%)	102 (44%)	120 (31%)	<.0001
<b>Rome IV functional gastrointestinal disorders</b>				
Functional esophageal disorders	346 (56%)	152 (66%)	194 (50%)	<.001
Functional chest pain	79 (13%)	33 (14%)	46 (12%)	.4
Functional heartburn	152 (25%)	71 (31%)	8 (21%)	.007
Globus	11 (2%)	1 (0.4%)	10 (3%)	.06
Functional dysphagia	259 (42%)	117 (51%)	142 (37%)	.001
Functional biliary disorders	7 (1%)	5 (2%)	2 (0.5%)	.1
Functional gastroduodenal disorders	431 (70%)	173 (75%)	258 (67%)	.04
Functional dyspepsia	348 (57%)	156 (67.5%)	192 (50%)	<.001
Postprandial distress syndrome	306 (50%)	145 (63%)	161 (42%)	<.001
Epigastric pain syndrome	199 (32%)	92 (40%)	107 (28%)	.002
Belching	70 (11%)	33 (14%)	37 (10%)	.08
Rumination	189 (31%)	73 (32%)	116 (30%)	.7
Chronic nausea and vomiting syndrome	89 (14%)	51 (22%)	38 (10%)	<.001
Cyclical vomiting syndrome	64 (10%)	30 (13%)	34 (9%)	.1
Functional bowel disorders	554 (90%)	205 (89%)	349 (91%)	.5
Irritable bowel syndrome	335 (54%)	137 (59%)	198 (51%)	.06
Functional constipation	76 (12%)	31 (13%)	45 (12%)	.5
Opiate-induced constipation	60 (10%)	21 (9%)	39 (10%)	.7
Functional diarrhea	34 (5.5%)	6 (3%)	28 (7%)	.01
Functional bloating and distension	17 (3%)	4 (2%)	13 (3%)	.23
Unspecified functional bowel disorder	60 (10%)	15 (7%)	45 (12%)	.04
Centrally mediated abdominal pain syndrome	3 (0.5%)	0 (0%)	3 (0.8%)	.3
Functional anorectal disorders	325 (53%)	138 (60%)	187 (49%)	.01
Fecal incontinence	100 (16%)	48 (21%)	52 (14%)	.02
Levator ani syndrome	114 (19%)	56 (24%)	58 (15%)	.005
Proctalgia fugax	180 (29%)	68 (29%)	112 (29%)	.9

### 3.3 | Odds ratio for FGIDs in HSD/hEDS subjects with POTS vs without POTS

The increased odds ratio for FGIDs in those HSD/hEDS subjects with POTS, compared to those without POTS, is shown in Table 2. Following adjustments for factors significant on univariate analysis (ie, age, chronic fatigue, fibromyalgia, and depression scores) the increased odds ratio for FGIDs among POTS-positive subjects remained essentially unaltered. Similarly, the unadjusted and adjusted odds ratio for experiencing gastrointestinal symptoms “at least one day per week” also remained increased in those with concomitant POTS (Table 3).

## 4 | DISCUSSION

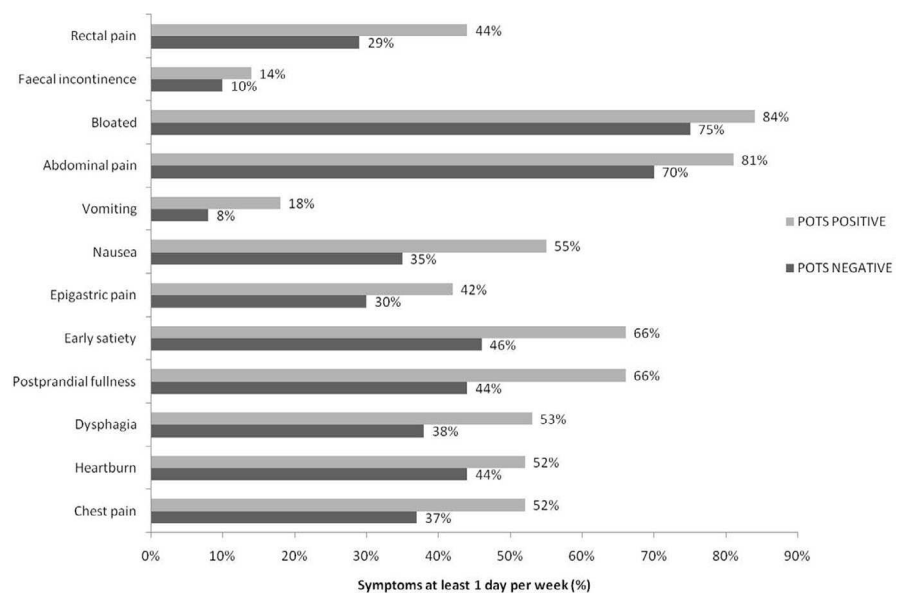
To our knowledge, this is the first study examining what impact concomitant POTS in HSD/hEDS has on the presence of Rome IV FGIDs and their symptom frequency. We show that, irrespective of POTS, almost all sampled individuals with HSD/hEDS fulfill diagnostic criteria for one or more FGIDs. However, in the third with POTS, the illness pattern appears further amplified as demonstrated by a greater prevalence of chronic fatigue, a trend toward increased fibromyalgia and elevated depression symptom scores, and greater presence of individual FGIDs—with increased symptom frequency—as well as more afflicted FGID regions. This presence of FGIDs, and GI symptom frequency, persists even after adjusting for potentially relevant factors.

The high prevalence of Rome IV FGIDs in HSD/hEDS has been described in a recent publication<sup>4</sup> and is in line with previous reports using historic criteria,<sup>5</sup> with relevant factors mediating this association being high somatic symptom reporting behavior and the use of opiates.<sup>4</sup> Our current analyses suggest that the co-presence of POTS is also associated with amplified gastrointestinal illness burden.

However, the literature is shrouded in uncertainty and controversy as to how POTS arises in HSD/hEDS and contributes toward the GI symptoms.<sup>15</sup> There is currently no biologically plausible pathophysiological mechanism to directly link HSD/hEDS with POTS.<sup>15</sup> Suggestions of laxity of blood vessels in hEDS/HSD as a cause of POTS speculative and devoid of evidence; notably, what argues further against such a mechanism is that POTS is rarely linked with vascular EDs.<sup>23</sup> Rather, the presence of POTS in HSD/hEDS has been hypothesized to arise as a secondary epiphenomenon, or as a common final pathway, due to the combination of commonly observed confounding factors seen in this cohort such as somatic hypervigilance, psychological distress, central sensitisation with behavioral amplification, physical de-conditioning, poor oral intake, and the use of drugs that can affect neuronal function and possess vasoactive properties (eg, opiates).<sup>8,15</sup> In fact, the management of POTS—while being outside the scope of this paper—does entail addressing the aforementioned factors.<sup>6</sup>

With regard to how POTS contributes toward GI symptoms, this may, in part, be due to autonomic dysfunction for which there is some, albeit limited, evidence.<sup>8-14</sup> However, the literature questions this as a sole mechanism given that dysautonomia would not readily explain: (a) why a proportion of individuals with POTS have such debilitating non-orthostatic GI symptoms, (b) why GI symptoms can persist despite the POTS being controlled, and (c) why “pain-related symptoms” are so pronounced throughout the GI tract.<sup>10</sup> An alternate hypothesis is that, in such instances, POTS is merely a bystander and that some of the proposed factors relevant to its genesis within HSD/hEDS are integral toward further exacerbating the dysfunctional brain-gut axis.<sup>8,15</sup> Further research is needed to disentangle this complex matrix and provide some clarity.

This study has a number of strengths. It adds to a body of smaller studies, as it is a large prospective examination of FGIDs defined according to the Rome IV criteria among select individuals with HSD/hEDS. Evaluating the members of the Ehlers-Danlos Support group



**FIGURE 1** The frequency of upper and lower gastrointestinal symptoms “at least one day per week” in subjects with HSD/hEDS with and without POTS. Note: All symptoms (except for fecal incontinence) were significantly more common in HSD/hEDS subjects with concomitant POTS than without POTS

**TABLE 2** The odds ratio for FGIDs in HSD/hEDS subjects with POTS vs without POTS

	Unadjusted odds ratio	Adjusted odds ratio <sup>a</sup>
Functional heartburn	1.7 (1.2-2.4)	1.6 (1.1-2.3)
Functional dysphagia	1.8 (1.3-2.4)	1.6 (1.1-2.3)
Functional dyspepsia	2.1 (1.5-2.9)	1.8 (1.3-2.7)
Postprandial distress syndrome	2.3 (1.7-3.3)	2.5 (1.5-3.1)
Epigastric pain syndrome	1.7 (1.2-2.4)	1.5 (1.0-2.2)
Chronic nausea & vomiting syndrome	2.6 (1.6-4.1)	2.4 (1.5-3.9)
Irritable bowel syndrome	1.4 (0.99-1.9)	1.3 (0.9-1.8)
Fecal incontinence	1.7 (1.1-2.7)	1.5 (0.96-2.4)
Levator ani syndrome	1.8 (1.2-2.7)	1.6 (1.1-2.5)

<sup>a</sup>Adjusted odds ratio controlling for age, depression, chronic fatigue syndrome, and fibromyalgia.

**TABLE 3** The odds ratio for experiencing gastrointestinal symptoms “at least one day per week” in HSD/hEDS subjects with POTS vs without POTS

	Unadjusted odds ratio	Adjusted odds ratio <sup>a</sup>
Rectal pain	1.9 (1.3-2.7)	1.7 (1.2-2.4)
Bloating	1.8 (1.2-2.8)	1.7 (1.1-2.6)
Abdominal pain	1.8 (1.2-2.7)	1.7 (1.1-2.5)
Vomiting	2.5 (1.5-4.2)	2.3 (1.3-3.8)
Nausea	2.2 (1.6-3.1)	1.9 (1.3-2.7)
Epigastric pain	1.7 (1.2-2.4)	1.5 (1.0-2.1)
Early satiety	2.3 (1.6-3.2)	2.1 (1.5-3.0)
Postprandial fullness	2.5 (1.8-3.5)	2.4 (1.6-3.5)
Dysphagia	1.8 (1.3-2.5)	1.6 (1.1-2.3)
Heartburn	1.4 (0.99-1.9)	1.2 (0.9-1.8)
Chest pain	1.9 (1.3-2.6)	1.7 (1.2-2.4)

<sup>a</sup>Adjusted odds ratio controlling for age, depression, chronic fatigue syndrome, and fibromyalgia.

captured individuals throughout the United Kingdom, as opposed to patients attending a single center. The questionnaire was promoted as a general health survey, and not GI-related, thus aiding efforts toward reducing selection bias. Furthermore, the online questionnaire platform had data verification, attention check, and repeat questions to ensure there were no missing data while also facilitating exclusion of inconsistent responders. However, there are appreciable limitations to our study. The presence of FGIDs was based on symptom reporting only and could not be verified by any tests to exclude organic GI disease. However, to partially compensate for this, we did exclude participants who disclosed a history of organic GI disease. We also cannot confirm or refute the self-reported doctor diagnosis of HSD/hEDS, POTS, chronic fatigue syndrome or fibromyalgia, as participants were anonymous and we had no access to

their medical records (eg, to check for autonomic function testing), and nor could we perform our own independent clinical evaluation. Finally, the response rate of 20% societal members may mean that our findings cannot necessarily be generalized to the wider HSD/hEDS community, although our cohort does resemble the severe clinical phenotype of HSD/hEDS patients attending clinical practice.<sup>24,25</sup> Moreover, the prevalence of POTS in HSD/hEDS was similar to that reported elsewhere in the literature, which lends support to our findings being clinically applicable.<sup>9</sup>

In conclusion, the high functional gastrointestinal disease burden in HSD/hEDS is further amplified in those with concomitant POTS. How POTS arises in HSD/hEDS, and is associated with increased GI symptoms, requires elucidation in future research.

#### ACKNOWLEDGMENT

The study was performed in accordance with the STROBE statement.

#### CONFLICT OF INTEREST

MS has received unrestricted research grants from Danone, Glycom, and Ferring Pharmaceuticals and served as a Consultant/Advisory Board member for AstraZeneca, Danone, Nestlé, Almirall, Allergan, Albireo, Glycom, and Shire, and as a speaker for Tillotts, Menarini, Takeda, Kyowa Kirin, Biocodex, AlfaSigma, Shire, Allergan, and Almirall. HT has served as Consultant/Advisory Board member for Almirall and Shire. OSP has received salary support from a research grants from Takeda Pharmaceuticals and Salix Pharmaceuticals and from a consulting agreement with Ironwood Pharmaceuticals and an educational grant provided by Takeda Pharmaceuticals and received a speaker honorarium in an educational program supported by Ironwood Pharmaceuticals and Takeda Pharmaceuticals. WEW received research grants from Takeda, Ironwood, Salix, and the Rome Foundation; served as a consultant to Biomerica USA, Ono Pharmaceuticals and Ferring; and received unrestricted educational grants from Takeda and Ferring. ADS has served as a consultant and speaker for Takeda-Israel and has received a research grant from them. FWDT, CL, and IA have no declarations.

#### AUTHOR CONTRIBUTIONS

IA, OSP, WEW, ADS, HT, and MS contributed to the study design and its conduct; FWDT, CYL, and IA analyzed the data and wrote the manuscript; all authors revised the manuscript and approved the final version of the article; IA is guarantor of the article.

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