


ORIGINAL ARTICLE

The prevalence and impact of orthostatic intolerance in young women across the hypermobility spectrum

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Abstract

Orthostatic intolerance (OI) is frequently reported in young women with generalized hypermobility spectrum disorder (G-HSD) and hypermobile EDS (hEDS). However, it remains currently unclear whether OI is a comorbidity or fundamental part of the pathophysiology of G-HSD or hEDS. This study investigated the prevalence and impact of OI in young women across the hypermobility spectrum. Forty-five women (14–30 years, 15 controls, 15 G-HSD, and 15 hEDS) undertook a head-up tilt (HUT) and active stand test. Postural Orthostatic Tachycardia Syndrome (POTS) and Orthostatic Hypotension (OH) were assessed using age-related criteria. Autonomic dysfunction and quality-of-life questionnaires were also completed. The prevalence of POTS was higher in women with G-HSD than hEDS and control groups during HUT (43% vs. 7% and 7%, respectively, $p < 0.05$), but similar between groups during the active stand (47%, 27%, and 13% for G-HSD, hEDS, and control, respectively). No participants had OH. hEDS and G-HSD participants reported more severe orthostatic symptoms and poorer quality of life than controls. Although POTS was observed in hypermobile participants, there is no conclusive evidence that its prevalence differed between groups due to differences between the HUT and active stand assessments. Nevertheless, OI and broader autonomic dysfunction impacted on their quality of life.

KEYWORDS

hypermobile Ehlers–Danlos syndrome, hypermobility spectrum disorder, joint hypermobility, postural orthostatic tachycardia syndrome, quality of life

1 | INTRODUCTION

Ehlers–Danlos syndrome (EDS) is a group of hereditary disorders that affects various connective tissues resulting in a number of comorbid features (Beighton et al., 1998). The hypermobile subtype is the most prevalent type of EDS (Beighton et al., 1998), and was traditionally considered a disorder of joint hypermobility and skin extensibility.

However, there is increasing recognition that it is also associated with non-musculoskeletal symptoms, including autonomic dysfunction (Castori et al., 2013; Rowe et al., 1999). In 2017, The International Consortium for EDS released new criteria for EDS classification, recognizing no candidate gene has been identified for hypermobile subtypes (Malfait et al., 2017). The new criteria for hypermobile EDS (hEDS) incorporate musculoskeletal, skin, and

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non-musculoskeletal features, including cardiovascular signs related to connective tissue laxity including mitral valve prolapse and aortic root dilatation (Malfait et al., 2017), although the incidence and severity of these structural cardiac abnormalities in individuals with hEDS are generally of little clinical significance (A. Hakim et al., 2017; Ritter et al., 2017). Generalized hypermobility spectrum disorder (G-HSD) which incorporates generalized joint hypermobility and musculoskeletal symptoms was also defined as a separate “non-syndromic” disorder (Castori et al., 2017) in an attempt to better understand the heterogeneity and likely multifactorial causes described in both the adult and pediatric hypermobility disorder populations (De Wandele et al., 2013; Pacey, Adams, et al., 2015). Despite increasing patient reports (Malfait et al., 2017) that autonomic symptoms, in particular orthostatic intolerance (OI), are experienced by people with hypermobility conditions (De Wandele et al., 2016; De Wandele, Rombaut, et al., 2014), the latter was not included in the 2017 diagnostic criteria due to the lack of experimental studies supporting OI as a defining feature of hEDS.

OI incorporates the presence of clinical signs (e.g., elevated heart rate) and symptoms (e.g., light-headedness/dizziness, palpitations, blurred vision and generalized weakness, and/or fatigue) when moving into the upright position, which are relieved by recumbency (Robertson et al., 1999). Orthostatic hypotension (OH) and postural orthostatic tachycardia syndrome (POTS) are the two main orthostatic syndromes. Both can be formally evaluated using a head-up tilt (HUT) test or active stand test. OH is characterized by a sustained fall in blood pressure (BP) within 3 min of standing (Freeman et al., 2011). POTS is a clinical syndrome that is characterized by a sustained and exaggerated increase in heart rate (HR) within 10 min of standing, in the absence of OH and accompanied by frequent orthostatic symptoms (Freeman et al., 2011; Sheldon et al., 2015). Self-report questionnaires are also particularly useful in clinical practice to evaluate the presence, frequency, and impact of orthostatic symptoms on function and day-to-day life.

Prior to 2017, a few studies (Clark et al., 2014; De Wandele, Calders, et al., 2014; De Wandele, Rombaut, et al., 2014; Gazit et al., 2003) had examined the prevalence of OI in people with hypermobility disorders. De Wandele, Rombaut, et al. (2014) investigated OI in 39 women with EDS hypermobile type (EDS-HT), which was the former diagnostic framework (Beighton et al., 1998) and 35 control subjects using a 20-min HUT. The prevalence of POTS was found to be greater in the EDS-HT (41%) than control (11%) group; the prevalence of OH was lower (~26%) but not significantly different between groups. The symptoms of OI were also more frequent and severe in the EDS-HT group.

Most previous studies examining OI in the EDS population have incorporated both males and females, a wide participant age range (e.g., 18–70 years, mean age ~35 years; Clark et al., 2014; De Wandele, Calders, et al., 2014; De Wandele, Rombaut, et al., 2014; Gazit et al., 2003) and no experimental studies have included people under 18 years of age. Many with EDS-HT, or Joint Hypermobility Syndrome (JHS) which are considered synonymous (Tinkle

et al., 2009), initially present with the condition in adolescence and early adulthood (Murray et al., 2013) and OI symptoms are reported to be common during the adolescent years in this patient group (Pacey, Tofts, et al., 2015). The presence of multisystemic symptoms, including OI, results in a trajectory of declining functional abilities over the following 3 years in children and adolescents with EDS-HT/JHS (Scheper et al., 2017). Indeed, many young hypermobile women report daily orthostatic symptoms to health professionals, which impact on their participation in vocational, educational, and everyday activities (Murray et al., 2013). To the best of our knowledge, there have been no prospective experimental studies which have specifically assessed OI in adolescents and young adults diagnosed using the 2017 criteria.

The aim of this study was to undertake a comprehensive analysis of OI in healthy young women (controls) and those diagnosed with G-HSD and hEDS. Because the new hEDS diagnostic criteria result in a more homogenous phenotype suggestive of broader connective tissue laxity than G-HSD, we hypothesized a higher prevalence of OI and more severe impact on quality of life in young women with hEDS than G-HSD and control participants.

2 | METHODS

2.1 | Editorial policies and ethical considerations

This study was approved by the Macquarie University Human Research Ethics Committee (HREC) and the Sydney Children's Hospitals Network HREC. It conformed to the standards set by the *Declaration of Helsinki*. All participants 16 years or older gave written informed consent; younger participants wishing to undertake the study had their parent or legal guardian sign the consent form.

2.2 | Participants

Participants were recruited from Macquarie University (NSW, Australia) and the wider University community, and a private rehabilitation clinic that specializes in the management of hypermobility conditions (Narrabeen Sports and Exercise Medicine Centre, NSW, Australia). For inclusion in this study, participants had to be between 14 and 30 years of age and non-smokers. As females account for more than 90% of the EDS-HT population (Beighton et al., 1998), we only included females in this study. Participants were excluded if they had non-structural cardiovascular disease, respiratory disease except mild asthma, neurological, or metabolic disease. Participants were also excluded if they were taking medication known to alter autonomic function (e.g., β -blockers or antihypertensive drugs) and not permitted by their physician to have their medication withheld for 3–5 days prior to the study. Participants confirmed that they were not pregnant and were studied within the early follicular phase (days 0–7) of their menstrual cycle or in their pill free days (oral contraceptive pill users).

2.3 | Experimental design

The study comprised (i) general health and joint hypermobility screening; (ii) physical testing of OI; and (iii) symptom, quality of life, and activity questionnaires.

2.3.1 | General health and joint hypermobility screening

Screening, and physical testing for OI, was conducted in a quiet, temperature-controlled (~21°C) laboratory at Macquarie University and commenced at approximately 9 am. Participants arrived at the laboratory having refrained from strenuous exercise for at least 24 h, and caffeine and alcohol for at least 12 h. They were also instructed to have a light breakfast, including fluid, on the morning of the study, and avoid having a hot (warm permitted) shower. No participants wore compression sportswear or other compressive garments. Participants with asthma were not studied if they had taken bronchodilator medications (e.g., β_2 -adrenergic receptor agonists) in the 4 h prior to testing.

Upon arrival at the laboratory, participants undertook anthropometric measures (height and weight), general health screening, and physical screening for the presence or absence of hEDS and G-HSD according to the revised 2017 diagnostic criteria (Castori et al., 2017; Malfait et al., 2017). After general health screening (e.g., questions about their personal and family history of cardio/cerebrovascular, respiratory, metabolic and musculoskeletal disease, medications, and general health), they underwent physical screening for current joint hypermobility (Beighton score), skin hyperextensibility, and arachnodactyly, and were questioned about historical joint hypermobility using the 5-point questionnaire (Hakim & Grahame, 2003). Participants who did not meet the new hEDS criteria (Malfait et al., 2017) were subsequently screened for the G-HSD using the 2017 framework for classification of joint hypermobility and related conditions (Castori et al., 2017). G-HSD was confirmed by the presence of a positive Beighton score plus one of more secondary musculoskeletal manifestations (e.g., macro- and/or micro-trauma, muscle weakness/disturbed proprioception, and other musculoskeletal traits; Castori et al., 2017). Based on the results, participants were assigned to one of three study groups (hEDS, G-HSD, and control participants). All participants who met or were close to the 2017 criteria for hEDS (Malfait et al., 2017) had their diagnosis confirmed by experienced physicians (LT and FC) specializing in the management of connective tissue disorders.

2.3.2 | Physical testing of OI

At the conclusion of general health and joint hypermobility screening, and having voided their bladder, participants were positioned in supine (on a tilt table) and instrumented for beat-to-beat measures of HR (3-lead electrocardiogram, ADInstruments, Colorado Springs

USA) and blood pressure (finger servonulling, vascular unloading [Peñáz] technique, Finometer, Finapres Medical Systems, Amsterdam, The Netherlands). The Finometer cuff was fitted on the left index or middle finger and referenced to heart level. The arterial waveform provided values for systolic and diastolic BP (SBP and DBP, respectively). Oscillometric BP measurements (SphygmoCor, XCEL, ATCOR Medical, Australia) were taken on the contralateral arm to periodically check and validate the Finometer BP measurements. During the experimental session, all data signals were recorded continuously at 1 kHz using an analog-to-digital converter (Powerlab/16SP ML795, ADInstruments) with commercially available software (LabChart version 8.1.17, ADInstruments) and stored for offline analysis.

After instrumentation and at the start of the experimental session, participants rested for at least 10 min, the final 5 min of which formed initial baseline data. Physical testing for OI involved HUT and active stand tests, in random order, with intervening rest. These tests were part of a wider suite of cardiac autonomic function tests. Before each test, participants rested for at least 8 min in supine. HUT from supine to 70 degrees was performed over 40 s with the participant then held at 70° HUT for 10 min. Active stand had the participant instructed to quickly (in approximately 3 s) assume an upright free-standing posture and remain there for 10 min. To limit the effect of the skeletal muscle pump, participants were instructed to remain as still as possible during the stand (and HUT).

Throughout both orthostatic challenges, participants were closely monitored and immediately returned to supine if they requested or were observed to be severely unwell. Participants were requested not to speak and to breathe normally throughout the tests. They used hand signals (right thumb up/down) to indicate how they felt. At the end of the tests, participants were asked to report any transient or sustained symptoms of OI (e.g., dizziness or, light-headedness, visual disturbance, chest tightness or palpitations, shortness of breath, nausea, tiredness) they had experienced during the stand/s but abated upon returned to supine.

2.3.3 | Data analysis

Cardiovascular parameters were assessed during the initial supine rest (averaged during the last 5 min), prior to undertaking the HUT and active stand (averaged during in the last 3 min before HUT or active stand), and throughout the 10-min orthostatic challenges. OH and POTS were defined according to the standard age-related criteria (Freeman et al., 2011; Sheldon et al., 2015; Skinner et al., 2010) as shown in Table 1. The changes in HR (i.e., HR increment), SBP, and DBP represented their average change (from baseline) over the last 4 min of HUT and active stand.

Initial orthostatic hypotension (IOH), defined as an exaggerated transient fall in BP immediately after standing (Wieling et al., 2007), was also measured and is defined in Table 1. IOH was identified from the nadir SBP and DBP responses within the first 15 s of active standing, taken from the moment the participant started moving.

TABLE 1 Definitions of orthostatic hypotension, initial orthostatic hypotension, and POTS

Category	Definition
Orthostatic hypotension	A sustained decrease in SBP of ≥ 20 mmHg or decrease in DBP of ≥ 10 mmHg within 3 min of standing (Freeman et al., 2011)
Initial orthostatic hypotension	A transient decrease in SBP of 40 mmHg and/or DBP of 20 mmHg within 15 s of active standing (Wieling et al., 2007)
POTS	Sustained and exaggerated increase in HR ≥ 30 beats·min ⁻¹ or absolute HR ≥ 120 beats·min ⁻¹ in adults over 19 years old (the HR increment is ≥ 40 beats·min ⁻¹ in individuals 12–18 years of age, inclusive; Skinner et al., 2010) in the absence of orthostatic hypotension and accompanied by frequent orthostatic symptoms (e.g., light-headedness, palpitations, blurred vision; Freeman et al., 2011; Sheldon et al., 2015).

Abbreviations: DBP, diastolic blood pressure; HR, heart rate; POTS, postural orthostatic tachycardia syndrome; SBP, systolic blood pressure.

2.3.4 | Symptom, quality of life, and activity questionnaires

Participants filled out the questionnaires independently the night before undertaking the single experimental session (screening and physical assessment of OI). Symptom (Orthostatic Grading Scale (Schrezenmaier et al., 2005) and Composite Autonomic Symptoms Score-31 (Sletten et al., 2012) and Quality of Life (Pediatric Quality of Life Inventory (Varni et al., 2001) for those ≤ 18 years of age, otherwise the RAND 36-Item Short Form Survey (Hays & Morales, 2001) questionnaires were completed online via a Qualtrics survey. Physical activity levels were assessed with the Activity Questionnaire for Adolescents and Adults (Chinapaw et al., 2009). These questionnaires were validated for use in adolescents and young adults, and relevant for use in both healthy individuals and patient populations. Details of each survey are as follows.

2.3.5 | Orthostatic Grading Scale

Symptoms of OI due to hypotension were quantified using the OGS (Schrezenmaier et al., 2005). The OGS is a well-validated OI questionnaire in patients with orthostatic hypotension (Schrezenmaier et al., 2005). It comprises five items which evaluate the frequency and severity of orthostatic symptoms, conditions of provocation, and how OI interferes with activities of daily living and standing time. Each item is graded on a severity scale of 0–4, to create a total score out of 20, with higher scores indicating greater severity or impact of symptoms.

2.3.6 | Composite Autonomic Symptoms Score

The severity and distribution of autonomic dysfunction were assessed using the COMPASS-31 questionnaire (Sletten et al., 2012). It comprises six domains which are assigned to: (i) OI (4 items); (ii) vasomotor (3 items); (iii) secretomotor (4 items); (iv) gastrointestinal (12 items); (v) bladder (3 items); and (vi) pupillomotor (5 items) symptoms (Sletten et al., 2012). The COMPASS is scored according to standardized guidelines (Sletten et al., 2012). The final domain scores are multiplied by weighting factors, which adjust for the relevance of a particular domain in assessing autonomic function; the weighting factor of 4.0 for OI domain is the highest (Sletten et al., 2012). The sum of all the weighted domain scores yields a total COMPASS score between 0 and 100, representing minimum and maximum autonomic symptoms scores, respectively. The COMPASS-31 has been shown to have excellent test–retest reliability, and internal validity, especially in the OI, vasomotor, gastrointestinal, and pupillomotor domains (Schultz et al., 2019; Treister et al., 2015) and has been validated in individuals with autonomic dysfunction (Ruška et al., 2018).

2.3.7 | Quality-of-Life Questionnaires

The Rand SF-36 (herein called SF-36) is a valid, reliable, and widely used generic instrument for assessing health-related quality of life in adults (Hays & Morales, 2001). The survey comprises 36 questions which assess eight domains of health-related quality of life, including (i) physical functioning; (ii) role limitations due to physical health; (iii) social functioning; (iv) bodily pain; (v) energy/fatigue; (vi) emotional well-being; (vii) role limitations due to emotional problems; and (viii) general health. The SF-36 is scored in two steps using standard scoring rules (Hays & Morales, 2001). The standard scoring algorithm for the eight domains combine to generate a domain score of 0–100 (where higher score indicates better health).

Although the SF-36 is valid for adults 18 years of age and older, we chose to use the Pediatric Quality of Life (PedsQL™ 4.0 Generic Core Scales Adolescent Version) in the 18-year-olds, as the questions are more appropriate for adolescents at school (James W Varni et al., 2001). The PedsQL™ 4.0 adolescent version is a generic health-related quality-of-life instrument that has been validated for 13- to 18-year-olds (Varni & Limbers, 2009; Varni et al., 2001). It assesses four domains of health-related quality of life (physical functioning, emotional functioning, social functioning, and school functioning). As per the guidelines (Varni & Limbers, 2009), the 23 items were reverse scored and linearly transformed to a scale of 0–100 (with 100 indicating higher quality of life). Scale scores are calculated as the sum of the items divided by the number of items answered. Summary scores for physical health (8 items) and psychosocial health (15 items) and total quality of life (all 23 items) were also calculated as the sum of the items divided by number of items.

2.3.8 | Activity Questionnaire for Adults and Adolescents

The AQuAA was specifically developed to assess both physical activity levels and sedentary behavior in adolescents and young adults (Chinapaw et al., 2009). The AQuAA questions are structured in five categories: (i) commuting activities; (ii) activity at work or school; (iii) household activities; (iv) leisure time activities; and (v) active sports. Participants recall the frequency (days), average time per day (hours and minutes), and perceived intensity (light, moderate, and intense) of activities in the past week (7 days), with age-specific examples to aid questionnaire completion (Chinapaw et al., 2009). For scoring, activities are assigned a metabolic equivalent of task (MET) value by using the Ainsworth compendium of physical activities (Ainsworth et al., 2000). The adolescent and adult MET cut-off values for sedentary (<2 METs, for both adolescents and adults), light (2–5 and 2–4 METs for adolescents and adults, respectively), moderate (5–8 and 4–6.5 METs for adolescents and adults, respectively), and vigorous (≥ 8 and ≥ 6 METs for adolescents and adults, respectively) physical activities are reported elsewhere (Chinapaw et al., 2009). Activities are then categorized, using the METs for each activity, into sedentary, light, moderate, and vigorous activity, and the sum of the time spent undertaking activity within each category reported in minutes per week.

2.4 | Statistical analysis

Continuous data are presented as means \pm standard deviation (SD) and categorical data as number (and %). All data were tested for normality using the Shapiro–Wilk test. All analyses were conducted using SPSS Version 26.0 (IBM SPSS Statistics, NY, IBM Corp). Significance was defined at an alpha level of 0.05 for all comparisons.

Between-group differences in continuous demographic data, cardiovascular parameters during the supine rest, and the results of the autonomic function, quality of life and activity scores, were assessed using a one-way analysis of variance (ANOVA) and the Bonferroni–Dunn test for post-hoc analysis.

Between-group differences in categorical variables were assessed using a Chi-squared test; when the minimum expected cell frequency was less than 5, a Fisher's Exact Probability test was used instead. In the case of significant associations between group and variable, a binomial test was used to compare proportions between groups.

A general linear model was used to investigate the within-group and between-intervention differences in baseline cardiovascular parameters before the HUT and active stand interventions, and changes in cardiovascular parameters. For each dependent variable, the model specified a main effect of intervention (HUT and active stand), a main effect for group (control, G-HSD, and hEDS) and an interaction (e.g., intervention \times group). Data were also analyzed with the difference in baseline HR between interventions as a covariate. Pearson's product–moment correlation coefficients were used to examine the relationship between the difference in baseline HR and the change in HR between interventions for each group.

3 | RESULTS

Of the 49 volunteers, 45 female participants met the criteria to be included in this study. Prior to screening, 30 identified as having a hypermobility-related condition. Where there was no relevant confirmation under the 2017 diagnostic criteria (Malfait et al., 2017), participants were reviewed by an expert clinician. Screening for the presence or absence of hypermobility conditions identified 15 participants who satisfied the criteria for hEDS, 15 who satisfied the criteria G-HSD and 15 control participants. Details of the percentage of participants in each group who met item level diagnostic criteria to detect the presence and absence of G-HSD and hEDS are shown in Table 2.

Participant demographics, anthropometric characteristics, general health screening data, AQuAA scores, and the resting cardiovascular parameters are listed in Table 3. There were no between-group differences in age, height, weight, and BMI; the analysis of variance was significant for age ($p = 0.038$), but the post-hoc tests were not significant ($p = 1.03$ and 0.06 for hEDS vs. control and G-HSD, respectively). Self-reported general health screening revealed that individuals with hEDS and G-HSD had a higher prevalence of fatigue, gastrointestinal disorders, anxiety and/or depression, and asthma than control participants. Individuals with hEDS also had a higher prevalence of severe headaches and/or migraines than control participants, and a higher prevalence of fatigue and gastrointestinal disorders than G-HSD participants. However, time spent undertaking sedentary, light, moderate, and vigorous activities were similar between groups. Resting cardiovascular parameters were comparable between groups and within the normal ranges. One individual with hEDS and one with G-HSD were on β -blocker medications and were permitted to have their medication withheld for 3–5 days prior to the study.

3.1 | Prevalence of POTS and orthostatic hypotension during HUT and active stand

The prevalence of OH during the HUT and active stand tests is shown in Table 4. No participants met the diagnostic criteria for OH during HUT or active stand. Most participants met the criteria for IOH (13 control, 10 G-HSD, and 14 hEDS), but there was no association between IOH and group (Chi-square = 0.75, $p = 1.00$, Cramer's $V = 0.14$).

During the HUT, more participants with G-HSD (6 [43%]) had POTS than hEDS (1 [7%]) and control (1 [7%]) participants (Table 4, Fisher's Exact Test = 7.0, $p = 0.04$, Cramer's $V = 0.44$). Numerically more participants had POTS during the active stand than HUT interventions (Table 4), with 2 control (13%), 7 G-HSD (47%), and 4 hEDS (27%) participants meeting criteria, although there was no association between the prevalence of POTS and group (Fisher's Exact Test = 3.90, $p = 0.16$, Cramer's $V = 0.3$).

To explore the importance of age on these findings, we ranked the participants by age and examined their HR increments during

TABLE 2 Details of the diagnostic criteria for classifying the presence or absence of G-HSD and hEDS

	Control (n = 15)	G-HSD (n = 15)	hEDS (n = 15)
Classification for hEDS^a			
Criterion 1—Generalized Joint Hypermobility			
Beighton Score (points out of 9)	1.7 ± 1.5	6.7 ± 1.3*	7.8 ± 1.4*
Beighton Score (≥5 points out of 9)	0 (0%)	15 (100%)	15 (100%)
Historical joint hypermobility (≥2 points out of 9)	1 (7%)	15 (100%)	15 (100%)
Participants who satisfy Criterion 1	1 (7%) ^c	15 (100%)	15 (100%)
Criterion 2 (≥ 2 of the following features)			
<i>Feature A (systemic manifestations)</i>			
- Soft velvety skin	1 (7%)	6 (40%)	10 (67%)
- Mild skin hyperextensibility	0 (0%)	6 (40%)	10 (67%)
- Unexplained striae	4 (27%)	3 (20%)	15 (100%)
- Bilateral piezogenic papules of the heel	7 (47%)	13 (76%)	14 (93%)
- Recurrent or multiple hernia (s)	1 (7%)	2 (13%)	0 (0%)
- Atrophic scarring	2 (13%)	4 (27%)	8 (53%)
- Prolapse (pelvic floor, rectum, or uterus)	0 (0%)	0 (0%)	0 (0%)
- Dental crowding and high or narrow palate	3 (20%)	6 (40%)	9 (60%)
- Arachnodactyly	4 (27%)	4 (27%)	7 (47%)
- Arm span to height ratio (≥1.05)	0 (0%)	0 (0%)	0 (0%)
- Mitral valve prolapse (confirmed with ECHO)	0 (0%)	1 (7%)	1 (7%)
- Aortic root dilatation with Z-score > +2	0 (0%)	0 (0%)	0 (0%)
<i>Participants who satisfy Feature A</i>	0 (0%)	0 (0%)	13 (87%)
<i>Feature B (positive family history)</i>			
≥ 1 first degree relative meeting current hEDS criteria	0 (0%)	0 (0%)	4 (27%)
<i>Participants who satisfy Feature B</i>	0 (0%)	0 (0%)	4 (27%)
<i>Feature C (musculoskeletal complications [≥1])</i>			
- Musculoskeletal pain ≥2 limbs, daily for 3 months	1 (7%)	6 (40%)	15 (100%)
- Chronic widespread pain (≥ 3 months)	1 (7%)	5 (33%)	13 (87%)
- Recurrent joint dislocations or frank joint instability	2 (13%)	8 (53%)	14 (93%)
<i>Participants who satisfy Feature C</i>	2 (13%)	8 (53%)	15 (100%)
Participants who satisfy Criterion 2	0 (0%)	0 (0%)	15 (100%)
Criterion 3 (meet all the following prerequisites)			
- Absence of unusual skin frailty	15 (100%)	15 (100%)	15 (100%)
- Exclusion of other heritable and acquired CTD	N/A	15 (100%)	15 (100%)
- Exclusion of alternative diagnoses	N/A	15 (100%)	15 (100%)
hEDS diagnosis (confirmed by physician)	0 (0%)	0 (0%)	15 (100%)
Classification for G-HSD^b			
Positive Beighton Score (≥5 points out of 9)	0 (0%)	15 (100%)	N/A
Secondary musculoskeletal manifestations (≥1)			
- Trauma (macro- and/or micro-trauma)	N/A	15 (100%)	N/A
- Chronic Pain	N/A	5 (33%)	N/A
- Disturbed proprioception	N/A	8 (53%)	N/A
- Other musculoskeletal traits	N/A	6 (40%)	N/A
G-HSD diagnosis	0 (0%)	15 (100%)	N/A

Note: Data are means (±SD) or number (and %). * $p \leq 0.05$ compared to control.

Abbreviations: G-HSD, generalized hypermobility spectrum disorder; hEDS, hypermobile Ehlers–Danlos Syndrome.

^aMalfait et al. (2017).

^bCastori et al. (2017).

^cOne participant, who met criterion 1, met no other criteria for hEDS or G-HSD.

TABLE 3 Demographic, general health screening, and resting cardiovascular data

	Control (n = 15)	G-HSD (n = 15)	hEDS (n = 15)
<i>Demographic data</i>			
Age (years)	23 ± 4	23 ± 4	19 ± 4
Height (m)	1.67 ± 0.06	1.67 ± 0.05	1.70 ± 0.05
Weight (kg)	64 ± 8	58 ± 7	63 ± 7
BMI (kg·m ⁻²)	23 ± 3	21 ± 2	22 ± 2
<i>General health screening</i>			
Structural heart defect	1 (7%) ^a	1(7%) ^b	1 (7%) ^b
Asthma	0 (0%)	6 (40%)*	5 (33%)*
Severe headaches and/or migraines	3 (20%)	8 (53%)	10 (67%)*
Gastrointestinal disorder	1 (7%)	9 (60%)*	14 (93%)***
Fatigue affecting daily living	3 (20%)	9 (60%)*	15 (100%)***
Anxiety and/or depression	2 (13%)	12 (80%)*	12 (80%)*
<i>AQuAA scores (minutes per week)</i>			
Sedentary activities	1903 ± 1240	2437 ± 1022	2762 ± 1260
Light activities	1232 ± 999	1780 ± 1200	1817 ± 1244
Moderate activities	588 ± 552	770 ± 575	478 ± 334
Vigorous activities	416 ± 420	365 ± 249	296 ± 267
<i>Cardiovascular parameters (at rest)</i>			
HR (beats·min ⁻¹)	63 ± 13	64 ± 11	69 ± 10
SBP (mmHg)	113 ± 11	110 ± 11	116 ± 9
DBP (mmHg)	61 ± 8	62 ± 6	66 ± 6

Note: Data are means (± SD) or number (and %). * $p < 0.05$ compared to control. ** $p < 0.05$ compared to G-HSD.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; G-HSD, generalized hypermobility spectrum disorder; hEDS, hypermobile Ehlers-Danlos Syndrome; HR, heart rate; SBP, systolic blood pressure.

^aSmall patent foramen ovale.

^bMild mitral valve prolapse. AQuAA, activity questionnaire for adults (18–55 years) and adolescents (≤ 18 years). Metabolic equivalent of task (MET) ranges for sedentary (< 2 MET's for both adolescents and adults), light (2–5 and 2–4 MET's in adolescents and adults, respectively), moderate (5–8 and 4–6.5 MET's in adolescents and adults, respectively), and vigorous (≥ 8 and ≥ 6.5 MET's in adolescents and adults, respectively) activities (as reported by Chinapaw et al., 2009). Cardiovascular parameters are a 5-min average taken during the initial supine rest.

HUT and active stand. A total of 14 participants were under 19 years of age, and the majority of these were in the hEDS group (8 [hEDS] vs. 3 [G-HSD] vs. 3 [control] participants). All groups had at least one participant who was under 19 years of age and did not sustain their age-related criteria for POTS (i.e., ≥ 40 b·min⁻¹), but nevertheless had a HR increment over 30 beats·min⁻¹ and were symptomatic during the HUT or active stand tests (Figure 1). Of note, three individuals with hEDS (two 16-year-old and one 18-year-old) fell into this category during the active stand.

To evaluate the impact of age on the diagnosis and prevalence of POTS, we also presented the number of participants who had a HR increment ≥ 30 beats·min⁻¹ in Table 4. Notably, in contrast to our results for POTS, there were no between-group differences when we categorized by HR ≥ 30 beats·min⁻¹, in HUT. In other words, categorization by HR increment or POTS diagnosis would change how we interpret the pattern of orthostatic responses across the hypermobility spectrum.

3.2 | Changes in cardiovascular parameters during HUT and active stand

Baseline cardiovascular parameters and changes in HR and BP prior to HUT and active stand are summarized in Table 5. The significant intervention effect for baseline HR, but nonsignificant group effect, indicates the resting HR in the 3 min immediately preceding the HUT and active stand were different (although still within normal limits); of note, there were no differences between the baseline HR prior to the HUT and initial resting HR. Examination of the individual data (not displayed) revealed more individuals with G-HSD (64%) and hEDS (67%) had a higher baseline HR before the HUT, compared to control participants (47%). Having a higher HR before HUT was not related to whether the HUT was undertaken before or after the active stand.

Table 5 also shows that there was no significant interaction for the changes in HR, indicating that the HR response to HUT and active stand was similar in the three groups. However, there was a

	Control	G-HSD	hEDS
HUT			
Number performed	15	14	15
POTS	1 (7%)	6 (43%)*	1 (7%)**
Sustained HR ≥ 30 beats·min ⁻¹	2 (13%)	6 (43%)	2 (13%)
Orthostatic hypotension	0 (0%)	0 (0%)	0 (0%)
Early stop of test	0 (0%)	0 (0%)	1 (7%)
Time of stop	-	-	2 min
Acute orthostatic symptoms	5 (33%)	9 (64%)	15 (100%)*,**
Active Stand			
Number performed	15	15	15
POTS	2 (13%)	7 (47%)	4 (27%)
HR ≥30 beats·min ⁻¹	5 (33%)	8 (53%)	7 (47%)
Orthostatic hypotension	0 (0%)	0 (0%)	0 (0%)
IOH	13 (93%)	10 (71%)	14 (93%)
Early stop of test	0 (0%)	1 (7%)	2 (14%)
Time of stop	-	5 min	4 and 4.5 min
Acute orthostatic symptoms	6 (40%)	11 (73%)	11 (73%)

TABLE 4 Prevalence of orthostatic intolerance and orthostatic symptoms during head-up tilt and active stand

Note: Data are numbers (and %). All control participants completed the HUT and active stand. One G-HSD participant choose not to undertake the HUT test. One hEDS participant terminated the HUT at 2 min, due to symptoms of presyncope. One G-HSD and two hEDS participants terminated the active stand test, also with presyncope symptoms. **p* ≤ 0.05 compared to control. ***p* ≤ 0.05 compared to G-HSD.

Abbreviations: G-HSD, generalized hypermobility spectrum disorder; hEDS, hypermobile Ehlers–Danlos Syndrome; HUT, head-up tilt; IOH, initial orthostatic hypotension; POTS, Postural Orthostatic Tachycardia Syndrome.

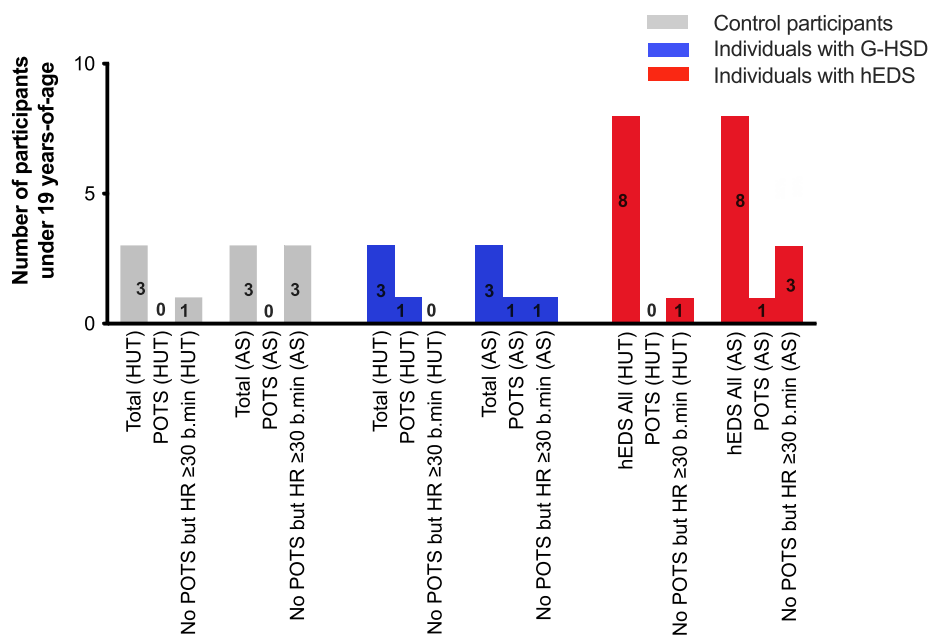


FIGURE 1 POTS and HR changes in participants under 19 years of age. AS, active stand; G-HSD, generalized hypermobility spectrum disorder; hEDS, hypermobile Ehlers–Danlos syndrome; HUT, head-up tilt

significant intervention effect, but non-significant group effect, indicating that the changes in HR were higher during the active stand than HUT in all groups. These findings align with our previous observation that, in all groups, more participants met the threshold for

POTS during the active stand than HUT. On the other hand, the changes in SBP and DBP were no different between groups or interventions and their small magnitude was consistent with the absence of OH (Table 5).

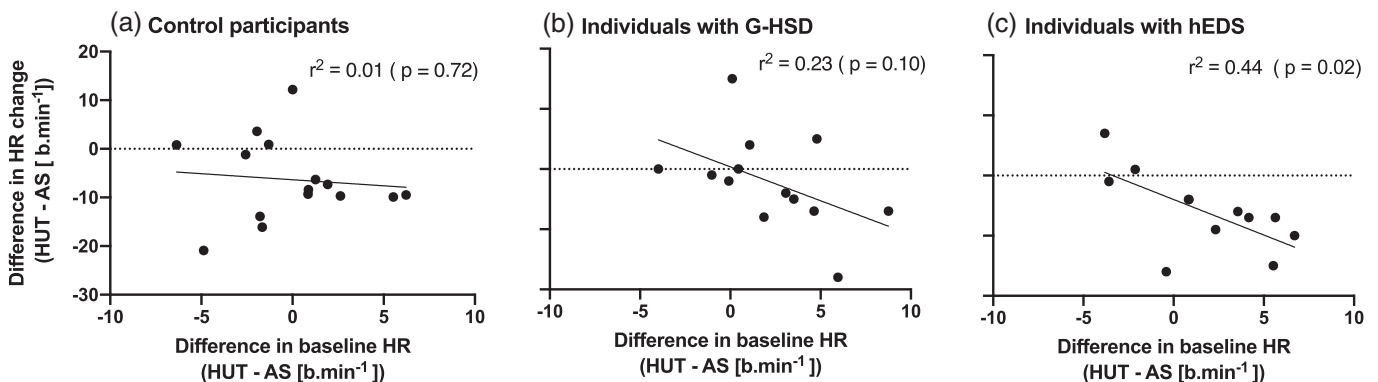
TABLE 5 Cardiovascular parameters before, and changes in cardiovascular parameters during, the head-up tilt and active stand interventions

	HUT			Active stand			p-values		
	Control (n = 15)	G-HSD (n = 14)	hEDS (n = 15)	Control (n = 15)	G-HSD (n = 15)	hEDS (n = 15)	Interaction	Intervention	Group
Baseline HR (beats·min ⁻¹)	62 ± 11	66 ± 12	70 ± 10	62 ± 11	63 ± 12	69 ± 10	0.21	0.025	0.18
Baseline SBP (mmHg)	115 ± 14	112 ± 11	117 ± 9	118 ± 10	110 ± 13	117 ± 8	0.41	0.67	0.20
Baseline DBP (mmHg)	64 ± 7	65 ± 6	65 ± 6	64 ± 7	64 ± 8	66 ± 5	0.66	0.92	0.62
HR (change) beats·min ⁻¹	20 ± 12	28 ± 12	24 ± 8	27 ± 13	31 ± 11	29 ± 19	0.31	0.001	0.36
SBP (change) mmHg	-5 ± 11	-7 ± 7	-9 ± 5	-7 ± 11	0.3 ± 11	-7 ± 10	0.21	0.26	0.44
DBP (change) mmHg	1 ± 7	1.4 ± 7	6 ± 5	3 ± 6	5 ± 9	5 ± 5	0.40	0.30	0.53

Note: Data are means ± SD. Baseline cardiovascular parameters are a 3-min average prior to each intervention. Generalized Linear Model was used to examine the Interaction (intervention time group), the Intervention (HUT or Active stand), and Group effects. Abbreviations: DBP, diastolic blood pressure; G-HSD, Generalized Hypermobility Spectrum Disorder; hEDS, hypermobile Ehlers-Danlos Syndrome; HUT, head-up tilt; HR, heart rate; SBP, systolic blood pressure.

Given the aforementioned findings, we considered whether a higher baseline HR before the HUT attenuated the change in HR during HUT. We, therefore, repeated the general linear model analysis

baseline HR. In other words, having a higher resting HR prior to the HUT appears to have attenuated the increase in HR during HUT, thereby significantly reducing the difference between the two inter-

**FIGURE 2** Correlations between the difference in baseline HR and difference in the changes in HR between HUT and active stand. AS, active stand; G-HSD, generalized hypermobility spectrum disorder; hEDS, hypermobile Ehlers-Danlos syndrome; HUT, head-up tilt

with the difference in baseline HR between interventions (HUT-active stand) as a covariate. Whilst the: i) intervention remained significant ($p = 0.004$); and ii) interaction (group \times intervention) and group effects remained non-significant ($p = 0.11$ and 0.18 , respectively), a significant interaction between the difference in baseline HR (HUT-active stand) and intervention ($p = 0.023$) was also revealed (not tabulated). This indicated that the higher baseline HR during HUT influenced the changes in HR during active stand and HUT, but its influence differed between groups.

Regression analysis was used to explore this further (Figure 2). Of note, individuals with hEDS who had a higher difference in baseline HR before the HUT than active stand had a smaller difference in the change in HR from baseline between HUT and active stand. Specifically, in the hEDS group, 44% of the difference in the changes in HR between the two interventions were explained by the difference in

interventions, and consequently resulting in differences in diagnosis for POTS in HUT. These relationships were not observed in the control or G-HSD groups.

3.3 | Symptoms of OI during HUT and active stand

Orthostatic symptoms were prevalent in all groups regardless of POTS diagnosis. All individuals with hEDS (100%) reported acute orthostatic symptoms during HUT, versus 64% in the G-HSD and 33% in the control groups (Table 4). The majority of individuals with hEDS and G-HSD also experienced orthostatic symptoms during active stand (73%, Table 4).

Figure 3 explores the type and frequency of self-reported symptoms during both the HUT and active stand. During the HUT,

dizziness was the most frequent symptom reported followed by headaches and palpitations (85%, 51%, and 34%, respectively). Dizziness was also the most frequently reported symptom during active stand but was followed by leg discomfort and visual disturbances (59%, 33%, and 30%, respectively).

3.4 | Autonomic symptoms and quality of life

The OGS and COMPASS-31 results are shown in Table 6. Individuals with hEDS, and to a lesser extent G-HSD, had higher total OGS scores than control participants. The total COMPASS-31 score, and the scores for most its subdomains including the OI domain, were also higher in individuals with hEDS and G-HSD than control participants.

The SF-36 results indicated that individuals with hEDS over 19 years of age had poorer physical functioning, more limitations due to physical health, more pain and fatigue, and poorer general health than G-HSD and control participants (Table 7). Individuals with hEDS also had lower scores for social functioning, emotional well-being, and its limitations, than control participants. Similarly, individuals with G-HSD had more fatigue and poorer emotional well-being than control participants; their limitations due to physical health also tended to be greater ($p = 0.057$ compared to control). The PedsQL results, also shown in Table 7, indicate that younger individuals with hEDS had poorer physical health and a lower PedsQL summary score than younger individuals with G-HSD and control participants.

4 | DISCUSSION

To the best of our knowledge, this is the first experimental study to comprehensively examine OI in a cohort of young women across

the hypermobility spectrum, using the 2017 international EDS classification. The main findings were as follows. First, during the HUT but not active stand, the objective diagnosis of POTS was more prevalent in individuals with G-HSD than individuals with hEDS and control participants. This led us to conclude there was no consistent pattern in the prevalence of POTS to discriminate between individuals with G-HSD and hEDS, due at least in part to (i) the impact of age on the POTS criteria; (ii) differences in quantifying POTS using passive and active orthostatic challenges; and (iii) whether or not participants prematurely ended the test, in which case POTS could not be measured. Second, in contrast to the physical measures, the acute symptoms of OI and their longer term impact of OI on the sufferer's quality of life revealed a clearer picture. Irrespective of POTS diagnosis, the majority of individuals with hEDS and G-HSD were symptomatic during the HUT and active stand. Moreover, in general, individuals with hEDS, and to a lesser extent G-HSD, reported more frequent and severe orthostatic symptoms, more widespread symptoms of autonomic dysfunction, and poorer quality of life than control participants. Collectively, these findings highlight the complexity and disconnect between the physiological and symptomatic impact of OI in young women across the hypermobility spectrum.

4.1 | Comparison with previous studies

Direct comparison with previous studies is difficult given differences in participant classification, participant selection, and method of assessing OI. Previous experimental studies have investigated OI in hypermobile participants across a wider age range using the old diagnostic criteria (De Wandele, Calders, et al., 2014; De Wandele, Rombaut, et al., 2014; Gazit et al., 2003), or presented retrospective analyses of cardiac autonomic function testing following reclassification of the participants

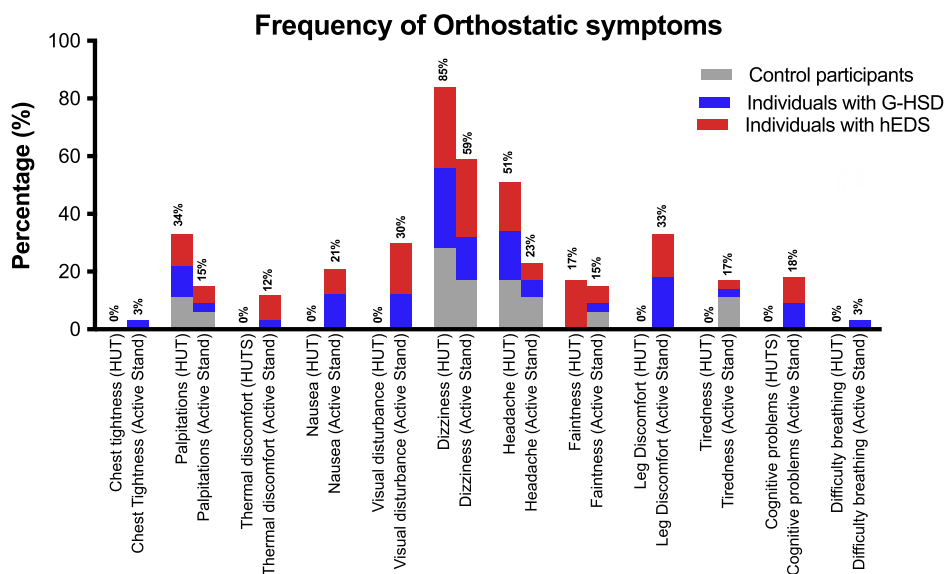


FIGURE 3 The frequency of acute orthostatic symptoms in control participants and individuals with G-HSD and hEDS during HUT and active stand. G-HSD, generalized hypermobility spectrum disorder; hEDS, hypermobile Ehlers-Danlos syndrome; HUT, head-up tilt

TABLE 6 Comparison of OGS and COMPASS 31 scores between groups

	Control (n = 15)	G-HSD (n = 15)	hEDS (n = 14)
Orthostatic Grading Scale			
Frequency of symptoms (0–4)	0.9 ± 0.8	1.9 ± 1.2*	2.6 ± 0.7*
Severity of symptoms (0–4)	1.0 ± 0.8	2.0 ± 1.2*	2.2 ± 0.6*
Conditions which provoke symptoms (0–4)	0.7 ± 0.7	1.4 ± 0.6*	2.0 ± 0.6***
Effect on Activities of Daily Living (0–4)	0.2 ± 0.4	0.8 ± 0.8 (p = 0.055)	1.5 ± 0.8***
Standing time (0–4)	0.2 ± 0.6	0.7 ± 0.7	2.1 ± 1.1***
TOTAL OGS Score (out of 20)	3.1 ± 2.7	6.8 ± 3.7*	10.4 ± 2.8***
COMPASS 31			
Orthostatic Intolerance Domain (max 40)	9.9 ± 4.7	16.5 ± 8.5*	22.3 ± 7.3*
Vasomotor Domain (max 5)	0.8 ± 0.0	1.4 ± 0.9	2.1 ± 1.0*
Secretomotor Domain (max 15)	0.3 ± 1.1	6.3 ± 3.9*	5.1 ± 4.4*
Gastrointestinal Domain (max 25)	4.3 ± 4.2	8.3 ± 4.6*	11.7 ± 4.5*
Bladder Domain (max 10)	0.0 ± 0.0	1.1 ± 1.9	2.5 ± 3.1*
Pupillomotor Domain (max 50)	1.2 ± 1.0	2.8 ± 1.0*	3.0 ± 1.5*
TOTAL COMPASS Score (out of 100)	16.4 ± 8.0	36.5 ± 15.8*	46.6 ± 14.4*

Note: Data are means (± SD). *p ≤ 0.05 compared to control. **p ≤ 0.05 compared to G-HSD.

Abbreviations: COMPASS 31, Composite Autonomic Symptom Score (31 items); G-HSD, generalized hypermobility spectrum disorder; hEDS, hypermobile Ehlers–Danlos Syndrome; max, maximum weighted score per domain; OGS, orthostatic grading scale.

TABLE 7 Comparison of quality-of-life scores between groups

	Control	G-HSD	hEDS
SF-36			
Number screened	12	12	6
Physical functioning	96 ± 10	76 ± 31	33 ± 18***
Role limitations due to physical health	92 ± 29	56 ± 44	8 ± 20***
Bodily pain	83 ± 27	67 ± 28	28 ± 15***
General health	67 ± 20	49 ± 27	20 ± 14***
Energy/fatigue	60 ± 14	33 ± 15*	8 ± 8**
Social functioning	90 ± 29	65 ± 20	38 ± 26*
Role limitations due to emotional problems	92 ± 29	58 ± 41	33 ± 42*
Emotional well-being	78 ± 10	57 ± 13*	44 ± 15*
PedsQL™ 4.0 Adolescent Version			
Number screened	3	3	8
Physical health (8 items)	90 ± 10	61 ± 27	38 ± 25*
Emotional functioning (5 items)	80 ± 5	58 ± 20	59 ± 22
Social functioning (5 items)	93 ± 8	87 ± 13	70 ± 22
Work/school functioning (5 items)	80 ± 20	53 ± 13	38 ± 26
Total summary score (23 items)	86 ± 9	65 ± 10	50 ± 20*
Physical health summary score (8 items)	90 ± 10	61 ± 27	38 ± 25*
Psychosocial health summary score (15 items)	84 ± 10	66 ± 4	56 ± 20

Note: Data are means (± SD). One hEDS participant did not complete the SF-36. *p ≤ 0.05 compared to control. **p ≤ 0.05 compared to G-HSD.

Abbreviations: G-HSD, generalized hypermobility spectrum disorder; hEDS, hypermobile Ehlers–Danlos Syndrome; PedsQL™, Pediatric Quality of Life Inventory 4.0 Generic Core Scales; SF-36, 36-item Short Form Health Survey questionnaire.

according to the new criteria (Celletti et al., 2020). There are also interstudy differences in the (i) sex mix of participants and (ii) grouping of hypermobile participants (e.g., EDS-HT/JHS and

hEDS/HSD) and duration of examining OI (e.g., 20 min vs. 10 min HUT). Nevertheless, there are several commonalities that warrants consideration.

As in previous studies, POTS was the most predominant hemodynamic phenotype of OI seen in the participants of this current study. Indeed, none of our participants met the criteria for OH. Previous research by De Wandele, Calders, et al. (2014) reported that the prevalence of POTS in individuals with EDS-HT was 41% after 20 min of HUT versus 26% for OH. The prevalence of POTS (and OH) during HUT was lower in individuals with hEDS in the present study (7%, during 10 min HUT). Although there were interstudy differences in the duration of the tilt, we believe the main reason for this difference is the stricter inclusion criteria for hEDS in the new classification system than EDS-HT using the Villefranche classification. In support of this notion, in 2020, Celletti and colleagues (Celletti et al., 2020) published a retrospective analysis of data from 102 participants who had been reclassified as having hEDS/HSD using 2017 criteria. They reported that 49% had POTS (and 4% had OH) after 20 min of HUT, which is largely consistent with the prevalence of POTS and OH during HUT in our G-HSD group (i.e., 43% and 0% for POTS and OH, respectively), despite our shorter duration tilt.

When interpreting these findings, it is also important to note several distinctions between our investigations and those of others that strengthen our results. First, our prospective study was specifically set up to investigate whether OI differentially impacted people with hEDS and G-HSD, rather than treating the two groups as a single entity. Second, our recruitment process did not intentionally seek participants who had known orthostatic symptoms, thereby reducing the potential for referral bias. Third, there is an increasing body of evidence that female sex hormones and diurnal rhythm influence orthostatic symptoms. OI is usually poorer in the morning than evening (Brewster et al., 2012) and healthy women and those with POTS are known to experience a greater incidence of orthostatic symptoms (e.g., light-headedness) in the early follicular phase (i.e., low concentration of estrogen and progesterone) versus late follicular and luteal phases (Fu et al., 2010; Muppa et al., 2013; Peggs et al., 2012). To optimize diagnostic sensitivity, all our participants were studied in the morning and in the first 7 days of their menstrual cycle (or hormone free days). By strictly controlling for diurnal changes and standardizing menstrual cycle phase, we also eliminated their confounding influence. No previous OI studies in the EDS population have controlled for these factors.

4.2 | OI across the hypermobility spectrum

Our study hypothesized that physical testing of OI would reveal a higher prevalence of OI, most likely POTS, in the hEDS than G-HSD group. This hypothesis arose because the stricter diagnostic criteria for hEDS suggest broader connective tissue laxity across more systems in the body in the hEDS than G-HSD groups. Although OI is not included amongst the systemic manifestations of hEDS within the current diagnostic criteria, the systemic manifestations (criterion 2) lend to the assumption that the ubiquitous collagen deficit is more clearly defined in hEDS. Thus, it seemed plausible that increased vascular compliance in individuals with hEDS than G-HSD could lead to greater

venous pooling upon standing and accordingly greater compensatory HR response. However, we did not observe a higher prevalence of POTS in the hEDS than G-HSD groups during the HUT or active stand. As there is no clear pattern in these responses, we consider there is insufficient evidence that the presence of POTS can be used to discriminate between individuals with hEDS and G-HSD.

Nevertheless, it is worth considering methodological differences which influence this interpretation.

4.2.1 | The influence of age on OI across the hypermobility spectrum

Age complicated our analysis because 14 participants were under 19 years of age and therefore required a higher HR increment to reach a POTS diagnosis than those ≥ 19 years. Whilst this was the correct clinical approach, the stringent application of these criteria may have been too simplistic. Half of the adolescent participants were aged 17–18 years and on the cusp of being considered adults, in which case the use of a $40 \text{ beats} \cdot \text{min}^{-1}$ “cut-off” could be considered somewhat arbitrary. Therefore, we took the more nuanced approach of examining their results both with and without the age-appropriate HR increments and with full consideration of their acute orthostatic symptoms, which were sometimes functionally disabling (i.e., led to termination of tilt). This approach is supported by Singer et al. (2012), who pointed out that the diagnostic criteria should be used judiciously and in combination with clinical judgment.

4.2.2 | Comparison of hemodynamic responses and diagnosis of POTS during HUT and active stand

An unexpected but important finding was that the HR increments were higher during the active stand than HUT. Although HUT and active stand are both acceptable challenges for assessing OI, HR increases are generally greater during HUT (Arnold et al., 2018; Plash et al., 2013). This is because active standing recruits the calf skeletal muscle pump to maintain body weight and postural stability (Verma et al., 2017). The skeletal muscle pump compresses the veins in the lower limb and plays a central role in minimizing the pooling of blood in the lower limbs and aiding venous return (Rowell, 1993). Accordingly, in contrast to passive standing, the reflex compensatory increase in HR to maintain cardiac output is lower during active stand (Plash et al., 2013).

Given the above, the question is now posed as to why our participants showed a greater increase in HR during the active versus passive stand, contrary to the expected physiology. Since we took care to ensure all participants were quiet, and minimized leg movement during both interventions, we have no reason to believe verbal stimuli or excessive muscle contraction differentially influenced the HR response to either challenge. It is possible that in individuals with G-HSD and hEDS, the higher HR prior to the HUT may have blunted the change in HR during testing, resulting in a greater increase in HR

during active stand. Somewhat simplistically, the increase in HR prior to the HUT may ensure a relatively greater cardiac output and greater peripheral resistance, which may have attenuated the venous pooling during HUT, thereby reducing the subsequent reflex-mediated increase in HR. In support for this argument: (i) the differences in the resting HR between the HUT and active stand were driven by the majority of individuals with G-HSD and hEDS having higher resting HR's before HUT; and (ii) differences in resting HR contributed to the differences observed in HR increments between HUT and active stand.

Anxiety may also have contributed to the higher HR prior to HUT. While not objectively tested multiple participants with G-HSD and hEDS reported more anxiety before the HUT because they feared that HUT would elicit orthostatic symptoms. Fisher et al. (2020) reported individuals with POTS, diagnosed using a tilt-table test, had heightened anxiety sensitivity compared to the general population. Their interpretation was that the heightened anxiety sensitivity, assessed by the Anxiety Sensitivity Index (Reiss et al., 1986), captured the fact that individuals with POTS perceived the HUT as a threat (Fisher et al., 2020). In light of the current findings, future research is needed to understand the complex interplay between acute psychological symptoms and OI in individuals with G-HSD and hEDS, prior to HUT and their impact on the subsequent HR increment during HUT.

Finally, the observation that the change in HR was higher during active stand has implications for assessing OI clinically. The active stand test was able to detect POTS at a greater rate than HUT, supporting the fact that active stand is a reasonable clinical test to use in this population. It also represents a more physiologically relevant method of assessing OI as it more closely replicates orthostatic challenges in daily living. Furthermore, active standing also affords the opportunity to study IOH, which was prevalent in all study groups.

4.2.3 | Autonomic dysfunction and health-related quality-of-life questionnaires

Despite the heterogeneity of findings in the HUT and active stand data, this study confirms that orthostatic symptoms and symptoms of broader autonomic dysfunction are frequently experienced by individuals with hEDS and, to a lesser degree, G-HSD. Moreover, the results from the quality-of-life surveys showed that quality of life was lower in individuals with G-HSD and hEDS, particularly in the physical functioning/health, bodily pain, general health, and energy and fatigue domains. These data align with previous research in the EDS-HT/JHS population (De Wandele, Calders, et al., 2014). Specifically, in support of our hypothesis, our self-report questionnaires generally revealed that orthostatic symptoms and their impact on quality of life were poorer in the hEDS, than G-HSD and control groups. These findings justify that the categorization of POTS does not explicitly characterize the prevalence of OI in the hypermobile population. This disconnect between symptomology and the presence of orthostatic tachycardia has been described in other populations (Lee et al., 2017; Schultz et al., 2019; Singer et al., 2012).

4.3 | Study limitations

The findings of this study need to be considered in view of several limitations. First, because this was a pilot study, the number of participants was relatively small. The small numbers reflect the real-world challenge of recruiting participants with rare disorders coupled with our strict recruitment criteria and methodological rigor. Nevertheless, this pilot study is suitably powered to detect significant differences in the prevalence of POTS among the three study groups for HUT. The required sample size is 39 participants (alpha level of 0.05, and $\beta = 0.9$) and we had a sample of $n = 45$. We acknowledge that the present study is underpowered to detect a significant difference in the prevalence of POTS during the active stand, as the required sample size for assessing POTS during an active stand would be 56 participants (alpha level of 0.05, $\beta = 0.9$).

Second, although the average age was no different between groups, there was a greater number of participants under 19 years of age in the hEDS group. Consequently, the hEDS group had a greater number of participants who required a 40 beats·min⁻¹ HR increment to meet the criteria for POTS. However, this imbalance has highlighted the impact of the age criteria on POTS diagnosis in hypermobile young women. Third, it could be argued that the 10-min duration of the HUT was not long enough to fully examine OI and a longer (e.g., 20 min) HUT should have been used. However, we chose to use a 10-min tilt for two reasons: (i) most recent studies (Arnold et al., 2018; Carew et al., 2009) argue that 10 min is sufficient, given the HR increase needs to be apparent within this time frame; and (ii) we did not want the testing session to be onerous, recognizing that fatigue is very common in individuals with G-HSD and hEDS (De Wandele et al., 2016; M. Roma, Marden, De Wandele, et al., 2018). Fourth, an unavoidable consequence of investigating young women between 14 and 30 years of age was that the younger participants undertook the pediatric quality-of-life scale, whereas our older ones undertook the SF-36. Nevertheless, there are sufficient commonalities in the domains that these differences do not influence the validity of our quality-of-life conclusions. Fifth, even though questions related to the participants' mental health (e.g., anxiety and depression) were included in our general health questionnaire, the participants' mental health was not formally assessed. The findings suggest that psychological factors may impact orthostatic tolerance, but future studies are needed to specifically elucidate the impact of psychological symptoms on orthostatic tolerance.

Finally, the AQuAA scores were similar between groups and the reported values similar to values previously reported for sedentary, light, and moderate activities (Chinapaw et al., 2009; van Markus-Doornbosch et al., 2019). However, the population in this study reported undertaking greater amounts of vigorous activity. This most likely reflects the fact that self-reported measures of activity are known to overestimate the time spent undertaking physical activity, in particular vigorous activity (Chinapaw et al., 2009; Oostdam et al., 2013). Indeed, for this reason, we primarily used the AQuAA to determine whether or not the participants in each group had similar activity levels. In other words, as demonstrated, we used the AQuAA to verify that the participants' fitness levels were controlled.

4.4 | Clinical significance

The present findings do not demonstrate a significant consistent difference in the prevalence of POTS among control, G-HSD, and hEDS participants when objectively assessed with physiological testing. Nevertheless, the self-reported clinical orthostatic symptoms and quality-of-life questionnaires clearly indicate the majority of young women with hEDS and to slightly lesser extent G-HSD experience profound and often incapacitating orthostatic symptoms, irrespective of a formal diagnosis of POTS. This discrepancy between objective and subjective findings highlights that solely relying on objective tests of OI fails to acknowledge the acute and long-term impact of OI on the lives of young hypermobile women. It reinforces the importance of incorporating both objective and subjective measures of OI when assessing for POTS in participants with hypermobile variants of EDS.

Our findings regarding the challenges in POTS diagnosis are not at odds with others exploring POTS in the wider population (Roma, Marden, & Rowe, 2018; Thijs et al., 2021). Rather they serve to reinforce concerns that the current diagnostic criteria for POTS are complicated by different thresholds for POTS depending upon the participants age and methodological issues (e.g., HUT versus active stand). These compound the discrepancies between symptomology and quality of life, and the stricter HR diagnostic criteria. Importantly, the current lack of a clear differentiation between the prevalence of POTS among control, G-HSD, and hEDS participants does not support the inclusion of objectively diagnosed POTS using HUT within the hEDS diagnostic criteria. Future work should continue to explore the influence and impact of OI across the hypermobility spectrum, particularly in young adult and adolescent participants, and understand the mechanisms for its debilitating symptoms.

5 | CONCLUSION

The findings of this study highlight that OI, specifically POTS, is prevalent in young women with G-HSD and hEDS. However, the results of the physical orthostatic challenges provide no clear evidence that any differences in prevalence exist between these groups, due at least in part to the impact of different POTS diagnostic criteria in our adolescent and adult population and the different responses to HUT and active stand challenges. Irrespective of diagnosis, the majority of our G-HSD and hEDS participants reported acute symptoms during HUT and active stand, which are often functionally disabling and impact on their quality of life. The findings of this study provide valuable guidance for future prospective studies investigating OI across the hypermobility spectrum, with larger numbers of participants.

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AUTHORS CONTRIBUTION

Conceptualization: Karen C. Peebles, Verity Pacey, Mark Butlin, and Alberto P. Avolio; Data curation: Karen C. Peebles and Isabella Tan; Formal analysis: Karen C. Peebles; Karen C. Peebles, Verity Pacey, Mark Butlin, and Isabella Tan interpreted results of experiments; Project administration: Karen C. Peebles, Original draft: Karen C. Peebles; Review and editing: Karen C. Peebles, Verity Pacey, Mark Butlin, Isabella Tan, Alberto P. Avolio, Felicity Collins, and Louise Tofts; Physician screening and clinical interpretation: Felicity Collins and Louise Tofts. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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