

RESEARCH

Open Access



Rates of mental health concerns among individuals assessed at the GoodHope Ehlers-Danlos Syndrome Clinic

P. Maxwell Slepian^{1,2,3,4,5*} , Kristina Axenova^{1,5}, Molly McCarthy^{1,2}, Rachel Siegal^{1,2}, Keisha Gobin^{5,6}, Aliza Weinrib^{1,2}, Stephanie Buryk-Iggers^{1,7}, Daniel Santa Mina^{1,2,7}, Laura McGillis¹, Nimish Mittal^{1,2}, Joel Katz^{1,2,3,5} and Hance Clarke^{1,2,3,4}

Abstract

Past research has indicated that individuals with Ehlers-Danlos Syndromes (EDS) and Generalized Hypermobility Spectrum Disorder (G-HSD) report psychological and psychiatric symptoms, particularly anxiety disorders and depressive symptoms, at much greater rates than the general population. However, these studies have been primarily conducted in small samples at European centres. We report a retrospective chart review from 1035 consecutive patients (88% female) assessed for EDS/G-HSD at the GoodHope EDS Clinic at Toronto General Hospital between June 2019 and June 2021. Prior to assessment, all patients completed self-reported mental health screening questions, the Inventory of Depressive and Anxiety Symptoms – Dysphoria scale, and the Borderline Symptom List-23. The majority of patients reported current or past anxiety or depressive symptoms (53–87%), and a substantial minority reported significant mental health concerns, including Posttraumatic Stress Disorder (4.7–34.8%), disordered eating (19%), self-harm (3–29.2%), and suicidal behaviour (7.8–18.6%). Patients did not differ by diagnostic category on self-report measures of dysphoria or borderline symptoms. Individuals with G-HSD reported higher rates of anxiety and depression in clinical interview than those diagnosed with non-hypermobility EDS, and endorsed a higher rate of having “struggled with anxiety or depression” on the mental health screening questionnaire than individuals not diagnosed with EDS/G-HSD. No other differences emerged across diagnostic groups. These findings highlight the need for psychological support for individuals with EDS or G-HSD.

Keywords Ehlers-danlos syndrome, Joint hypermobility, Hypermobility spectrum disorder, Psychology, Anxiety

Introduction

Ehlers-Danlos Syndromes (EDS) and Generalized Hypermobility Spectrum Disorder (G-HSD) are a group of hereditary connective tissue disorders that are typically associated with a range of physiological features including unstable joints that easily sublux/dislocate, stretchy/fragile skin, and organ/systemic dysfunction [1]. These features are associated with myriad symptoms and comorbid conditions, including chronic pain and recurrent acute pain, gastrointestinal distress, dysautonomia, and respiratory symptoms [1]. Among these common comorbidities, a number of psychological disorders have

*Correspondence:

P. Maxwell Slepian
maxwell.slepian@uhn.ca

¹GoodHope Ehlers-Danlos Syndrome Clinic, Toronto General Hospital, 11 PMB 100D, 200 Elizabeth St, Toronto, ON, CA M5G 2C4, Canada

²Department of Anesthesia and Pain Management, Toronto General Hospital, Toronto, Ontario, Canada

³Department of Anesthesiology and Pain Medicine, University of Toronto, Toronto, Ontario, Canada

⁴Krembil Research Institute, University Health Network, Toronto, Ontario, Canada

⁵Department of Psychology, York University, Toronto, Ontario, Canada

⁶St. Joseph's Healthcare, Hamilton, Canada

⁷Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, Canada



© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

also been noted to commonly co-occur with EDS/G-HSD [2–4].

Recognition that psychological symptoms are an important aspect of EDS/G-HSD emerged out of clinical observation [2]. Initial reports focused primarily on anxiety symptoms in individuals diagnosed with Joint Hypermobility Syndrome (JHS), based on the Beighton Criteria [5, 6]. These studies identified higher rates of panic disorder, agoraphobia, and simple phobias in individuals with JHS compared to controls recruited from a rheumatology clinic [5, 6]. Further case-controlled studies have confirmed an association between hypermobility and anxiety disorders, and have also linked hypermobility to an increased risk of major depression [7]. Case reports have also linked EDS/G-HSD with disordered eating; and studies of psychiatric populations have identified greater hypermobility among individuals diagnosed with anxiety, ADHD, or psychosis compared to controls [3].

However, there are notable limitations in these studies. Given the rapidly changing definitions and diagnostic criteria for EDS and hypermobility [1], the majority of these studies were conducted using dated diagnostic criteria, particularly for JHS, which is no longer recognized by the International EDS Consortium as a clinical diagnosis [7]. Findings from these studies continue to be generalized to EDS/G-HSD without re-evaluation in the context of the 2017 diagnostic criteria. Moreover, the case-control approach taken in the majority of these studies rarely reflects the medical complexity typically seen in EDS/G-HSD. That is, comparison groups do not control for symptoms such as pain and dysautonomia that are also linked to psychological distress [5, 6].

Recently, the GoodHope Ehlers-Danlos Syndrome Clinic was established at Toronto General Hospital [8]. This multi-disciplinary program was established for the purpose of timely diagnosis and management to improve lives of people living with EDS and G-HSD. Patients suspected to have EDS or hypermobility are referred by family physicians or other specialists. Diagnostic experts conduct detailed clinical assessment, physical examination and order genetic testing if necessary. Patients who are diagnosed with any subtype of EDS or G-HSD are then advised a comprehensive treatment plan including visits to subspecialty EDS physicians (pain medicine, gastroenterology, respirology, cardiology, allergy and immunology) and professionally-guided self-management programs (psychology, physiotherapy and rehabilitation, dietitian, and social work). As part of the program intake, all patients are asked about mental health history and complete several validated self-report measures focused on mental health. The current study is a retrospective analysis of individuals assessed at the GoodHope EDS Clinic and aims to describe rates of mental health concerns and identify whether mental health concerns

differ by diagnostic group; non-hypermobility EDS, hEDS, G-HSD, or not diagnosed with EDS/G-HSD (i.e. no signs of hypermobility or collagen dysfunction).

Methods

Participants

Participants include all consecutive patients assessed at the GoodHope Ehlers-Danlos Syndrome (EDS) Clinic between June 2018 and June 2021 as part of a retrospective chart review. A total of 1035 patients (88% female) were assessed at the GoodHope EDS clinic over the study period outlined, making them eligible for inclusion.

Procedure

Patients from across Ontario were referred to the GoodHope EDS clinic by family physicians or other specialists for assessment of suspected EDS or G-HSD. As part of the intake process, patients completed self-report measures of mental health prior to their initial visit to the clinic. During their initial assessment, the physician or nurse practitioner took a detailed medical and social history, including questions on mental health history. A physical examination focused on identifying markers of hypermobility and connective tissue dysfunction was then performed. If necessary, patients were referred for genetic testing at this time. Following this assessment, (and genetic testing where applicable) patients were diagnosed with EDS, G-HSD or were found not to meet the 2017 EDS criteria and discharged from the program.

Measures

Mental health history was assessed using two methods. The first was an in-house, self-report screening measure that asked participants to respond (Yes/No) to the following questions: (1) “Have you ever struggled with anxiety or depression”, (2) “Have you ever taken medication for anxiety/depression”, (3) “Have you ever had an eating disorder”, (4) “Do you now or have you in the past suffered from Post-Traumatic Stress Disorder”, (5) “Have you ever hurt yourself on purpose”, (6) “Have you ever tried to end your life”, (7) “Have you ever spent time in the hospital for psychiatric care”, and 7) “Have you ever had treatment for mental health in the past?”. Second, patients were asked in a clinical interview if they had a history (Yes/No) of anxiety, depression, Post-Traumatic Stress Disorder, Obsessive-Compulsive Disorder, or a personality disorder.

Dysphoria was assessed using the Inventory of Depressive and Anxiety Symptoms – Dysphoria subscale (IDAS-D) [9]. The IDAS-D is 10-item a scale demonstrating a strong ability to screen for the presence of internalizing psychopathology [10] – specifically relevant to general distress (i.e., dysphoria). Empirically-established cut-offs on the IDAS-D have been identified to screen for likely

internalizing disorder, and a cut-off score of 28.5 was determined to maximize diagnostic specificity. Moreover, the IDAS-D is a more sensitive and specific screening measure than commonly-used scales such as the Beck Depressive Inventory – II and the Beck Anxiety Inventory [10].

Emotion dysregulation was assessed using the Borderline Symptom List (BSL-23) [11]. The BSL-23 is a well-established self-report instrument based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders 5th Edition for the revised diagnostic criteria for borderline personality disorder (BPD), the experiences of both clinical experts, and BPD patients. This instrument is used to assess the severity of 23 feelings and experiences typically reported by BPD patients [11]. Items are averaged to create a final score with higher score indicative of higher levels of borderline psychopathology. In the current sample, the alpha coefficient value is 0.95 for the BSL-23 – reflecting excellent internal consistency. A clinical cut-off score of 1.5 has been recommended to discriminate between individuals with BPD and other clinical populations [12].

Pain, fatigue, and physical function were assessed using the Multidimensional Health Assessment Questionnaire (MDHAQ) [13]. The MDHAQ includes single numerical ratings scales measuring pain due to illness in the past 2 weeks, from 0, *no pain*, to 10, *pain as bad as it could be*, and a single item measuring fatigue over the past week, from 0, *fatigue is not a problem*, to 10, *fatigue is a major problem*. The MDHAQ also includes 10 items assessing physical function (e.g. “Get in and out of bed”) on a 4-point Likert scale, from 0, *without any difficulty*, to 3, *unable to do*. Items are summed and then divided by 3 to create a final score that ranges from zero to 10, with higher scores indicating poorer physical function [13]. The physical function subscale demonstrated excellent internal consistency in the current sample, $\alpha = 0.90$.

The Composite Autonomic Symptom Score-31 (COMPASS 31) was used to assess self-reported autonomic dysfunction. The COMPASS-31 is a 31-item questionnaire consisting of six domains: orthostatic intolerance (4 items), vasomotor dysfunction (3 items), secretomotor dysfunction (4 items), gastrointestinal system dysfunction (12 items), bladder dysfunction (3 items), and pupilomotor dysfunction (5 items) [14]. Patients are asked to rate the presence, frequency, and severity of symptoms. The total score ranges from 0 to 100, with higher scores indicating greater autonomic dysfunction.

Data analysis

For the purposes of the current study, physician/NP diagnosis was simplified into four diagnoses, hEDS, G-HSD, non-hypermobility EDS subtypes diagnoses, not-EDS/G-HSD (i.e. not diagnosed with EDS or G-HSD).

Non-hypermobility EDS subtypes were combined into a single diagnostic group to allow for quantitative analysis of mental health concerns and, unlike hEDS which can be diagnosed only by clinical assessment, all of these individual syndromes have a known genetic mechanism of collagen dysfunction. These subtypes were combined in analyses as previous has indicated that individuals with genetically-confirmed EDS experience higher quality of life and lower mental health symptoms than individuals with hEDS [15]. Chi-square tests were used to examine differences in binary mental health variables by diagnostic category. Pairwise chi-squared tests were used to follow-up significant omnibus tests. Within each group of follow-up tests, a Bonferroni correction was used to control family-wise Type I error rate (i.e., 0.05/number of tests). A series of one-way analyses of variance (ANOVAs) was used to examine differences in symptom severity between non-hypermobility EDS, hEDS, G-HSD, and not-EDS/G-HSD.

Results

Sample characteristics

A summary of sample characteristics is presented in Table 1. Of the 1035 consecutive cases reviewed, 42 (4.1%) were diagnosed with a non-hypermobility EDS (Classical EDS, $n = 18$; Classical-like EDS, $n = 2$; Vascular EDS, $n = 16$; Arthrochalasia EDS, $n = 1$; Kyphoscoliotic EDS, $n = 2$; Musculocontractural EDS, $n = 1$; Periodontal EDS, $n = 2$), 81 (7.8%) were diagnosed with hEDS, 410 (39.6%) were diagnosed with G-HSD, and 502 (48.5%) were not to meet diagnostic criteria for EDS or G-HSD (i.e. not-EDS/G-HSD). Across diagnostic categories, the average age was 35.4 years ($SD = 11.9$), and the majority were female sex (88.5%). Education, employment, and marital status are described in Table 1. Pairwise comparisons indicated that individuals with non-hypermobility EDS subtypes and those with not-EDS/G-HSD were older at the time of their initial EDS clinic visit than those with hEDS or G-HSD, all p 's < 0.008. There was a greater proportion of males among individuals with non-hypermobility EDS than any other diagnostic category, all p 's < 0.001. Pain intensity (partial $\eta^2 = 0.02$), fatigue (partial $\eta^2 = 0.02$), and autonomic dysfunction (partial $\eta^2 = 0.04$) differed by diagnostic category, all p 's < 0.05. Follow-up pairwise tests with Bonferroni correction indicated that individuals with hEDS, G-HSD, and not-EDS/G-HSD reported greater pain, fatigue, and autonomic dysfunction than individuals with non-hypermobility EDS, all p 's < 0.008.

Mental health screening questionnaire

Table 2 describes rates of mental health concerns for the overall sample and by diagnostic category. Across groups, there was a high prevalence of depression/

Table 1 Sample characteristics

	Total Sample (n = 1035)	Non-hypermobile EDS (n = 42)	hEDS (n = 81)	G-HSD (n = 410)	Not diagnosed EDS/G-HSD (n = 502)	P-value
Sex, n (%)						
Female	916 (88.5)	27 (64.3)	75 (92.6)	372 (90.7)	442 (88)	<0.001**
Male	119 (11.5)	15 (35.7)	6 (7.4)	38 (9.3)	60 (12)	
Age, Mean, SD	35.3 (12)	39.6 (13.9)	33.02 (10.5)	33.16 (11.1)	36.96 (12.3)	<0.001**
Education Level, n (%) ^a						
High School	195 (22)	11 (32.4)	19 (26)	88 (24.4)	77 (18.4)	0.06
College/University	551 (62.2)	19 (55.9)	38 (52.1)	214 (59.3)	280 (70)	
Post-Graduate	140 (15.8)	4 (11.8)	16 (21.9)	59 (16.3)	61 (14.6)	
Employment Status, n (%) ^b						
Disability/Benefits	259 (26.8)	10 (26.3)	20 (25.3)	97 (24.5)	132 (29.1)	0.34
Employed	439 (45.4)	23 (60.5)	39 (49.4)	176 (44.4)	201 (44.3)	
Homemaker	66 (6.8)	1 (2.6)	3 (3.8)	26 (6.6)	36 (7.9)	
Looking for work	47 (4.9%)	1 (2.6)	5 (6.3)	24 (6.1)	17 (3.7)	
Student	156 (16.1)	3 (7.9)	12 (15.2)	73 (18.4)	68 (15)	
Marital Status, n (%) ^c						
Common law	108 (11.3)	3 (8.3)	13 (16.9)	40 (10.4)	52 (11.3)	0.15
Divorced	33 (3.5)	2 (5.6)	3 (3.9)	15 (3.9)	13 (2.8)	
Married	323 (33.8)	19 (52.8)	19 (24.7)	118 (30.7)	167 (36.4)	
Separated	25 (2.6)	1 (2.8)	1 (1.3)	8 (2.1)	15 (3.3)	
Single	462 (45.3)	11 (30.6)	41 (53.2)	202 (52.6)	208 (45.3)	
Widowed	5 (0.5)	0 (0)	0 (0)	1 (0.3)	4 (0.9)	
Beighton Score, Mean (SD)	3.9 (2.2)	3.5 (2.6)	6.1 (1.7)	5.2 (1.4)	2.4 (1.6)	<0.001**
Pain ^d	5.9 (2.4)	4.5 (3.1)	6.3 (2.0)	6.0 (2.1)	5.9 (2.6)	<0.001**
Fatigue ^d	7 (2.6)	5.2 (3.4)	7.0 (2.6)	7.3 (2.4)	6.9 (2.7)	0.001**
Physical Function ^d	2.7 (1.8)	2.1 (2.0)	2.9 (1.9)	2.7 (1.8)	2.7 (1.8)	0.157
Autonomic Dysfunction ^e , Mean (SD)	26.7 (9.3)	18.6 (12.6)	26.9 (7.7)	28.0 (8.7)	26.61 (9.4)	0.002**

Notes. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; ^aMissing $n = 149$; ^bMissing $n = 68$; ^cMissing $n = 79$ ^dFrom Multidimensional Health Assessment Questionnaire Total $n = 950$, non-hypermobile EDS $n = 37$, hEDS $n = 74$, G-HSD $n = 384$, Not diagnosed EDS/G-HSD $n = 455$; ^eAutonomic Dysfunction Total $n = 401$, non-hypermobile EDS $n = 14$, hEDS $n = 31$, G-HSD $n = 166$, Not diagnosed EDS/G-HSD $n = 190$

anxiety (87.5%), disordered, eating (19%), PTSD (34.8%), self-harm (29.2%), and suicidal behavior (18.6%). Patients differed by diagnostic category in rate of endorsing “have you ever struggled with anxiety or depression”, $X^2(3, n = 781) = 15.03, p = 0.002$, “have you ever taken medication for anxiety or depression”, $X^2(3, n = 781) = 8.08, p = 0.04$, “have you ever hurt yourself on purpose”, $X^2(3, n = 781) = 8.87, p = 0.03$. Follow-up pairwise tests indicate that individuals diagnosed with G-HSD had greater odds of having “struggled with anxiety or depression” than those not diagnosed with EDS/G-HSD, $OR = 2.39, X^2(1, n = 688) = 12.35, p < 0.001$, or those with non-hypermobile EDS subtypes, $OR = 3.72, X^2(1, n = 361) = 7.49, p = 0.006$. No other pairwise comparisons were significant with Bonferroni correction.

Clinician history

Table 3 describes rates of mental health diagnoses reported during clinician history taking for the total sample and by diagnostic category. Across diagnostic groups, the majority of patients reported anxiety (62%) and depression (53%), whereas a smaller proportion of patients reported PTSD (4.7%), personality disorders (1.5%), obsessive-compulsive disorder (2.1%), history of

suicide attempts (1.9%), current suicidal ideation (7.8%), and self-harm (3%). Patient reported history of anxiety, $X^2(3, n = 1035) = 4.36, p = 0.002$, and depression, $X^2(3, n = 1035) = 10.16, p = 0.017$, differed by diagnostic category. Follow-up pairwise tests indicated that individuals diagnosed with G-HSD had greater odds of reporting a past diagnosis of depression, $OR = 2.77, X^2(1, n = 448) = 8.91, p = 0.003$, or anxiety, $OR = 3.07, X^2(1, n = 448) = 11.77, p = 0.001$, than individuals with non-hypermobile EDS subtypes. No other pairwise comparisons were significant with Bonferroni correction. There were no differences by diagnostic category in patient reported history of PTSD, personality disorder, Obsessive Compulsive Disorder, all p 's > 0.05 .

Dysphoria

Patient scores on the IDAS-D did not differ by diagnostic category, $F(3,741) = 1.05, p = 3.68$. Self-reported dysphoria was also evaluated using a diagnostic cut off for likely internalizing disorder (IDAS-D > 28.5). Across groups, a large minority of patients (43.4%) screened positive for likely internalizing disorder. There were no differences in rates of likely internalizing disorder among individuals with hEDS (36%), non-hypermobile EDS (40.9%),

Table 2 Rates of mental health concerns reported on mental health screening questionnaire

	Total Sample (n = 781)	Non-hypermobile EDS (n = 26)	hEDS (n = 67)	G-HSD (n = 335)	Not diagnosed EDS/G-HSD (n = 353)	P-value
1) Have you ever struggled with anxiety or depression?						
Yes	683 (87.5)	20 (47.6)	57 (85.1)	310 (92.5)	296 (83.9)	0.002**
No	98 (12.5)	6 (23.1)	10 (14.9)	25 (7.5)	57 (16.1)	
2) Have you ever taken medication for anxiety or depression?						
Yes	553 (70.8)	14 (53.8)	45 (67.2)	252 (75.2)	242 (68.6)	0.044*
No	228 (29.2)	12 (46.2)	22 (32.8)	83 (24.8)	111 (31.4)	
3) Have you ever had an eating disorder?						
Yes	148 (19)	3 (11.5)	17 (25.4)	72 (21.5)	56 (15.9)	0.097
No	633 (81)	23 (88.5)	50 (74.6)	263 (78.5)	297 (84.1)	
4) Do you now or have you in the past suffered from Post-Traumatic Stress Disorder?						
Yes	272 (34.8)	6 (23.1)	21 (31.3)	126 (37.6)	119 (33.7)	0.351
No	509 (65.2)	20 (76.9)	46 (68.7)	209 (62.4)	234 (66.3)	
5) Have you ever hurt yourself on purpose?						
Yes	228 (29.2)	4 (15.4)	23 (34.3)	112 (33.4)	89 (25.2)	0.031*
No	553 (70.8)	22 (84.6)	44 (65.7)	223 (66.6)	264 (74.8)	
6) Have you ever tried to end your life?						
Yes	145 (18.6)	3 (11.5)	15 (22.4)	62 (18.5)	65 (18.4)	0.682
No	636 (81.4)	23 (88.5)	52 (77.6)	273 (81.5)	288 (81.6)	
7) Have you ever spent time in the hospital for psychiatric care?						
Yes	144 (18.4)	3 (11.5)	14 (20.9)	65 (19.4)	62 (17.6)	0.687
No	637 (81.6)	23 (88.5)	53 (79.1)	270 (80.6)	291 (82.4)	
8) Have you ever had treatment for mental health in the past?						
Yes	470 (60.2)	13 (50.0)	38 (56.7)	209 (62.4)	210 (59.5)	0.530
No	311 (39.8)	13 (50.0)	29 (43.3)	126 (37.6)	142 (40.5)	

Note. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

G-HSD (44.4%), or those not diagnosed with EDS/G-HSD (43.4%), $X^2(3, n = 745) = 0.85, p = 0.84$. Scores on the IDAS-D are summarized in Table 4.

Borderline symptoms

Patient reported borderline symptoms did not differ by diagnostic category, $F(3,749) = 2.18, p = 0.09$. Borderline symptoms were also evaluated using a diagnostic cut-off score (1.5), that has been found to distinguish individuals with BPD from other clinical populations. Approximately one-fifth of the sample (20.1%) screened positive for likely BPD. There were no differences in rates of likely borderline personality disorder among individuals with hEDS (16.9%), non-hypermobile EDS subtypes (7.7%), G-HSD (22.5%), or not-hEDS/GHSD (19.5%), $X^2(3, n = 750) = 4.1, p = 0.25$. Scores on the BSL-23 are summarized in Table 4.

Discussion

The current study presents a retrospective review of mental health concerns among patients assessed at the GoodHope Ehlers-Danlos Syndrome Program between July, 2019 and June, 2021. As part of an assessment for EDS and hypermobility, patients were asked to

self-report on mental health history and complete measures of dysphoria and borderline personality disorder symptoms. Patients universally reported extremely high rates of mental health concerns. 87.5% reported a history of anxiety or depression. Moreover, the report of a history of PTSD, disordered eating, self-harm, and current or past suicidal ideation, and history of suicide attempts were all well above lifetime prevalence of these disorders in the general population [16]. Likewise, on symptom self-report (IDAS-D, BSL-23), a large minority of patients scored above empirically identified screening cut-offs, despite the use of the most specific empirically-validated cut scores [10, 12]. Indeed, 43.4% of patients scored above the cut-off for likely internalizing disorder on the IDAS-D, and 20.1% of patients scored above the cut-off for likely Borderline Personality Disorder. Notably, patient reported mental health history much less frequently during clinical interview compared to self-report screening or symptom measures. However, even these lower rates greatly exceed population norms. These findings highlight both the frequency and severity of mental health concerns for individuals undergoing evaluation for EDS and hypermobility.

Table 3 Rates of mental health diagnoses from clinician history note

	Total Sample (n = 1020)	Non-hypermobile EDS (n = 40)	hEDS (n = 81)	G-HSD (n = 408)	Not diagnosed EDS/G-HSD (n = 491)	P-Value
Anxiety						
Yes	632 (62.0)	16 (40.0)	46 (56.8)	274 (66.8)	296 (60.3)	0.002**
No	388 (38.0)	24 (60.0)	35 (43.2)	134 (32.7)	195 (39.7)	
Depression						
Yes	541 (53.0)	13 (32.5)	40 (49.4)	233 (57.1)	255 (51.9)	0.017*
No	479 (47.0)	27 (67.5)	41 (50.6)	175 (42.9)	236 (48.1)	
PTSD						
Yes	48 (4.7)	0 (0)	3 (3.7)	23 (5.6)	22 (4.5)	0.391
No	972 (95.3)	40 (100.0)	78 (96.3)	385 (94.4)	469 (95.5)	
Personality Disorder						
Yes	15 (1.5)	0 (0)	0 (0)	8 (2.0)	7 (1.4)	0.477
No	1005 (98.5)	40 (100.0)	81 (100.0)	400 (98.0)	484 (98.6)	
Obsessive Compulsive Disorder						
Yes	21 (2.1)	0 (0)	0 (0)	9 (2.2)	12 (2.4)	0.400
No	999 (97.9)	40 (100.0)	81 (100.0)	399 (97.8)	479 (97.6)	
Past Suicide Attempts						
Yes	19 (1.9)	0 (0)	1 (1.2)	12 (2.9)	6 (1.2)	0.201
No	1001 (98.1)	40 (100.0)	80 (98.8)	396 (97.1)	485 (98.8)	
Current Suicidal Thoughts/Ideation						
Yes	80 (7.8)	2 (5.0)	9 (11.1)	29 (7.1)	40 (8.1)	0.570
No	940 (92.2)	38 (95.0)	72 (88.9)	379 (92.9)	451 (91.9)	
History/Current Self-Harm						
Yes	31 (3.0)	1 (2.5)	2 (2.5)	15 (3.7)	13 (2.6)	0.814
No	989 (97.0)	39 (97.5)	79 (97.5)	393 (96.3)	478 (97.4)	

* $p < 0.005$, ** $p < 0.01$, *** $p < 0.001$ **Table 4** Dysphoria and Borderline symptoms by diagnosis

	Total Sample	Non-hypermobile EDS	hEDS	G-HSD	Not diagnosed EDS/G-HSD	P-value
Dysphoria^a						
Total Score, Mean (SD)						
% above Clinical Cutoff (N)	27.0 (9.7)	23.8 (10.3)	26.4 (9.2)	27.2 (9.5)	27.1 (10.0)	0.57
	43.4 (323)	36 (9)	40.9 (27)	44.4 (142)	43.4 (145)	0.84
Borderline Symptoms^b						
Mean Score (SD)	0.88 (0.8)	0.52 (0.5)	0.89 (0.7)	0.91 (0.8)	0.88 (0.75)	0.09
% above Clinical Cutoff (N)	20.1 (151)	7.7 (2)	16.9 (11)	22.5 (73)	19.5 (65)	0.25

Notes. * $p < 0.005$, ** $p < 0.01$, *** $p < 0.001$; ^aDysphoria Total $n = 745$, non-hypermobile EDS $n = 25$, hEDS $n = 66$, G-HSD $n = 320$, Not diagnosed EDS/G-HSD $n = 334$;^bBorderline Symptoms Total $n = 750$, non-hypermobile EDS $n = 26$, hEDS $n = 65$, G-HSD $n = 325$, Not diagnosed EDS/G-HSD $n = 334$

Whereas the majority of individuals with EDS or G-HSD reported mental health concerns, differences between diagnostic subgroups and those not diagnosed with EDS/hypermobility were less pronounced than in previous research [2]. In our sample, individuals diagnosed with G-HSD had greater odds of reporting a history of anxiety/depression than individuals with non-hypermobile EDS subtypes or those not diagnosed with EDS/hypermobility. There were no significant differences in rates of any other mental health diagnosis or on self-reported symptom severity measures. This is in contrast to the vast majority of prior reports, which identified higher rates of mental health disorders among individuals with EDS/G-HSD compared to matched controls [2, 7]. Indeed, even where there were significant differences (e.g. anxiety and depression) in this study, the effect size

of these differences was much smaller than that reported in the past. There are several potential reasons why diagnostic groups in the present study did not differ in mental health concerns. It may be that such differences were not identified because data collection was not optimized for identification of mental health concerns. It may also be a reflection of cultural or systemic differences due to study of geographically restricted samples, both in this study and previous research. However, it is also possible that those not diagnosed with EDS/hypermobility in the present study represent a more well-matched comparison cohort that used in previous studies. These patients were all referred to the GoodHope EDS Clinic specifically for evaluation of possible EDS or hypermobility and in many cases this referral was due to presence of comorbidities common in EDS/G-HSD. Further research using

control groups matched on multiple symptom measures (e.g. pain, autonomic dysfunction, dysphoria) are needed to isolate the relationship between collagen dysfunction or hypermobility and mental health outcomes.

The similarity in mental health concerns between individuals with EDS/G-HSD and those not diagnosed with EDS or G-HSD does not preclude the possibility of a unique mechanism underlying mental health concerns among individuals with EDS/G-HSD. However, if this is the case, the mechanism does not appear to be captured by the Beighton Score, which is the primary measure of hypermobility in the 2017 international diagnostic criteria [1, 17]. Future research should examine more nuanced relationships between connective tissue disorders and mental health symptoms. There are also several plausible shared mechanisms underlying the high levels of distress among patients assessed during this time period. In particular, other medical concerns, such as pain or autonomic dysfunction impacted individuals across diagnostic categories and are known to exacerbate psychological distress [10]. Indeed, these variables have been previously reported to be strongly associated with psychopathology among individuals with EDS/G-HSD [18, 19]. In the current study, these symptoms did not differ between individuals with hypermobility (hEDS, G-HSD) and those with chronic widespread pain and no hypermobility. In addition to these distressing medical symptoms, individuals with EDS/G-HSD often report a long history of invalidation from medical providers, friends, and family [20]. This invalidation can exacerbate symptoms such as pain [21], and has likely been experienced for many years, given that many individuals with EDS/G-HSD go 10 or more years from symptom onset to diagnosis. It is likely as well that those individuals who were referred to our clinic and did not receive a diagnosis of EDS or G-HSD have had many similar experiences. Future studies should focus on experimental and longitudinal evaluation of these putative mechanisms to identify novel and specific treatment targets for individuals with these complex medical concerns.

Given the prevalence of mental health concerns in this population, it is critical to provide mental health support to patients with EDS and G-HSD as a standard part of a multidisciplinary care approach. Research on efficacy of specific psychological interventions for EDS/G-HSD is limited, but there is a developing evidence base supporting cognitive-behavioral therapy as a self-management approach as well as third-wave behavior therapies (e.g. ACT, Acceptance and Commitment Therapy; DBT, Dialectic Behavior Therapy) [22]. At the GoodHope EDS Clinic, we provide a stepped-care treatment approach incorporating ACT and DBT in groups and individual psychotherapy focused on symptom management and adjustment to chronic illness [8]. However, it

is important that providers take a patient-centred and trauma-informed approach to reduce stigma when referring patients with EDS or G-HSD to mental health services. Patient interest in such referrals may be limited due to perceptions that this implies symptoms are psychogenic [23].

There are several notable limitations to this study. First, these data do not include gold-standard mental health diagnoses. In the case of “likely” Borderline Personality Disorder in particular, we do not believe that high scores on this self-report measure represent true diagnosis, but instead is likely to capture emotion dysregulation associated with general distress, pain, and autonomic dysfunction. All mental health information was collected as part of a medical diagnostic evaluation with the goal of screening to facilitate referral to the GoodHope EDS Clinic psychology program [8]. The encounter in which the patient history taking occurred was a clinical encounter and not standardized for research. It is likely that there was substantial variation in how questions were asked and the exact timing of when measures were completed. It is also notable that there are potential biases in both self-report and clinician interview when assessing mental health as both are subject to recall bias and patients are potentially more likely to self-report than disclose to a clinician [23]. As data collection was not designed with this study in mind, only limited demographic information was collected. Moreover, the structure of these appointments changed after the beginning of the COVID-19 pandemic in March, 2020. In order to reduce face-to-face contact, the history component of the diagnostic appointment was separated from the physical exam and was conducted using secure telehealth programming. The physical exam then occurred at a later date. From a statistical perspective, many fewer patients were diagnosed with non-hypermobility EDS and hEDS than other diagnoses and statistical tests utilizing these categories should be interpreted with caution. Despite these limitations, this retrospective analysis included a large cohort of individuals with EDS/G-HSD and a well-matched comparison group. Future studies within the GoodHope EDS Clinic will focus on prospective evaluation of mental health and the impact of psychological intervention for individuals with EDS or G-HSD.

In conclusion, the vast majority of patients assessed at the GoodHope EDS Clinic reported mental health concerns in at least one domain. Indeed, rates of reported mental health diagnoses among all individuals assessed at the GoodHope EDS Clinic were well above the lifetime prevalence of these disorders in the general population. However, rates of mental health concerns largely did not differ between those diagnosed with EDS/G-HSD and those for whom EDS/G-HSD were ruled out but presented with a complex medical history including chronic

pain. Future research should seek to determine if there are unique mechanisms underlying mental health concerns in EDS/G-HSD that could point to population specific treatment options.

Abbreviations

BPD	Borderline personality disorder
BSL	Borderline symptom list
EDS	Ehlers-danlos syndrome
G-HSD	Generalize hypermobility spectrum disorder
hEDS	hypermobility ehlers-danlos syndrome
IDAS-D	Inventory of depressive and anxiety symptoms – dysphoria scale
MDHAQ	Multidimensional health assessment questionnaire
NP	Nurse practitioner
PTSD	Posttraumatic stress disorder
REB	Research ethics board

Acknowledgements

Not applicable.

Author contributions

P. Maxwell Slepian: Conceptualization, data management, analysis, writing – original draft; Kristina Axenova: writing – review and editing; Molly McCarthy: conceptualization, writing – review and editing; Rachel Siegal: conceptualization, writing – review and editing; Keisha Gobin: data management, writing – review and editing; Aliza Weinrib: Conceptualization, writing – review and editing; Stephanie Buryk-Iggers: data management, writing – review and editing; Daniel Santa Mina: writing – review and editing; Nimish Mittal: Conceptualization, writing – review and editing; Laura McGillis: conceptualization, writing – review and editing; Joel Katz: conceptualization, writing – review and editing; Hance Clarke: conceptualization, writing – review and editing.

Funding

No funding was received for the research reported in this manuscript.

Data availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are stored in controlled access data storage at University Health Network.

Declarations

Ethics approval and consent to participate

This research was approved by the Research Ethics Board (REB) of the University Health Network in Toronto, Canada (REB# 18-5850). Consent waiver was granted due to retrospective nature of study and no potential risk of harm to participants.

Consent for publication

Not applicable.

Competing interests

The authors declare they have no competing interests.

Received: 5 August 2024 / Accepted: 7 January 2025

Published online: 14 February 2025

References

- Malfait F, Francomano C, Byers P, et al. The 2017 international classification of the Ehlers–Danlos syndromes. *Am J Med Genet Part C: Seminars Med Genet.* 2017;175(1):8–26.
- Bulbena A, Baeza-Velasco C, Bulbena-Cabr e A, et al. Psychiatric and psychological aspects in the Ehlers–Danlos syndromes. *Am J Med Genet Part C: Seminars Med Genet.* 2017;175(1):237–45.
- Bulbena-Cabr e A, Baeza-Velasco C, Rosado-Figuerola S, Bulbena A. Updates on the psychological and psychiatric aspects of the Ehlers–Danlos syndromes and hypermobility spectrum disorders. *Am J Med Genet Part C: Seminars Med Genet.* 2021;187(4):482–90.
- Sinibaldi L, Ursini G, Castori M. Psychopathological manifestations of joint hypermobility and joint hypermobility syndrome/Ehlers–Danlos syndrome, hypermobility type: the link between connective tissue and psychological distress revised. *Am J Med Genet Part C: Seminars Med Genet.* 2015;169(1):97–106.
- Bulbena A, Dur o JC, Porta M, et al. Anxiety disorders in the joint hypermobility syndrome. *Psychiatry Res.* 1993;46(1):59–68.
- Bulbena A, Duro J, Mateo A, Porta M, Vallejo J. Joint hypermobility syndrome and anxiety disorders. *Lancet.* 1988;332(8612):694.
- Smith TO, Easton V, Bacon H, et al. The relationship between benign joint hypermobility syndrome and psychological distress: a systematic review and meta-analysis. *Rheumatology.* 2014;53(1):114–22.
- Mittal N, Mina DS, McGillis L, et al. The GoodHope Ehlers Danlos Syndrome Clinic: development and implementation of the first interdisciplinary program for multi-system issues in connective tissue disorders at the Toronto General Hospital. *Orphanet J Rare Dis.* 2021;16(1):1–9.
- Watson D, O'Hara MW, Chmielewski M, et al. Further validation of the IDAS: evidence of convergent, discriminant, criterion, and incremental validity. *Psychol Assess.* 2008;20:248–59. <https://doi.org/10.1037/a0012570>.
- Stasik-O'Brien SM, Brock RL, Chmielewski M, et al. Clinical utility of the inventory of depression and anxiety symptoms (IDAS). *Assessment.* 2019;26(5):944–60. <https://doi.org/10.1177/1073191118790036>.
- Bohus M, Kleindienst N, Limberger MF, et al. The short version of the Borderline Symptom List (BSL-23): development and initial data on Psychometric Properties. *PSP.* 2009;42(1):32–9. <https://doi.org/10.1159/000173701>.
- Kleindienst N, Jungkunz M, Bohus M. A proposed severity classification of borderline symptoms using the borderline symptom list (BSL-23). *Borderline Personality Disorder Emot Dysregulation.* 2020;7(1):11. <https://doi.org/10.1186/s40479-020-00126-6>.
- Pincus T, Yazici Y, Bergman M. Development of a multi-dimensional health assessment questionnaire (MDHAQ) for the infrastructure of standard clinical care. *Clin Exp Rheumatol.* 2005;23(5 Suppl 39):S19–28.
- Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W. COMPASS 31: a Refined and Abbreviated Composite Autonomic Symptom score. *Mayo Clin Proc.* 2012;87(12):1196–201. <https://doi.org/10.1016/j.jmayocp.2012.10.013>.
- Baeza-Velasco C, Rodriguez N, Parra L, Guti errez-Rosado T. Adjustment to disease and quality of life in people with vascular Ehlers–Danlos and Loeys-Dietz syndromes: a mixed-method study. *Front Psychol.* 2023;14. <https://doi.org/10.3389/fpsyg.2023.1019863>.
- KESSLER RC, ANGERMEYER M, ANTHONY JC, et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry.* 2007;6(3):168–76.
- Castori M, Tinkle B, Levy H, Grahame R, Malfait F, Hakim A. A framework for the classification of joint hypermobility and related conditions. *Am J Med Genet Part C: Seminars Med Genet.* 2017;175(1):148–57. <https://doi.org/10.1002/ajmg.c.31539>.
- Wasim S, Suddaby J, Parikh M, et al. Pain and gastrointestinal dysfunction are significant associations with psychiatric disorders in patients with Ehlers–Danlos syndrome and hypermobility spectrum disorders: a retrospective study. *Rheumatol Int.* 2019;39(7):1241–8.
- Hershenfeld SA, Wasim S, McNiven V, et al. Psychiatric disorders in Ehlers–Danlos syndrome are frequent, diverse and strongly associated with pain. *Rheumatol Int.* 2016;36(3):341–8.
- Bennett SE, Walsh N, Moss T, Palmer S. Understanding the psychosocial impact of joint hypermobility syndrome and Ehlers–Danlos syndrome hypermobility type: a qualitative interview study. *Disabil Rehabil.* 2021;43(6):795–804.
- Vangronsveld KL, Linton SJ. The effect of validating and invalidating communication on satisfaction, pain and affect in nurses suffering from low back pain during a semi-structured interview. *Eur J Pain.* 2012;16(2):239–46. <https://doi.org/10.1016/j.ejpain.2011.07.009>.
- Song JZ, Luong D, Feldman ECH, et al. Psychological interventions for individuals with Ehlers–Danlos syndrome and hypermobility spectrum disorder: a scoping review. *Orphanet J Rare Dis.* 2023;18(1):254. <https://doi.org/10.1186/s13023-023-02799-y>.
- Halverson CME, Cao S, Perkins SM, Francomano CA. Comorbidity, misdiagnoses, and the diagnostic odyssey in patients with hypermobile

Ehlers-Danlos syndrome. *Genet Med Open*. 2023;1(1):100812. <https://doi.org/10.1016/j.gimo.2023.100812>.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.