The psychological burden associated with Ehlers-Danlos syndromes: a systematic review

Context: Ehlers-Danlos syndromes (EDS) are disorders of connective tissue that lead to a wide range of clinical presentations. While we are beginning to understand the association between EDS and psychological manifestations, it is critical that we further elucidate the relationship between the two. Understanding the correlation between EDS and mental health will better ensure swift diagnosis and effective treatment for patients.

Objectives: This study aims to systematically examine and report the prevalence of psychiatric disorders in the EDS population.

Methods: The PubMed database was searched on June 14, 2021 for articles published from January 2011 to June 2021. We included original, evidence-based, peer-reviewed journal articles in English that reported information on psychiatric disorders among EDS patients. Psychiatric disorders and psychological conditions were limited to those included in the “psychology” and “mental disorders” Medical Subject Headings (MeSH) search terms defined by the National Library of Medicine. Publications identified utilizing this search strategy by M.K. were imported into the Covidence system, where they first underwent a title and abstract screening process by three independent reviewers (M.K., K.L., H.G.). During the full-text review, two independent reviewers read the full text of the questionable articles to assess their eligibility for inclusion. Studies were excluded if they did not meet our target objective or if they were not in English or if they were opinion pieces, conference abstracts, or review articles. Data were extracted from the shortlisted studies by reviewers. During the data extraction phase, the quality and risk of publication bias were assessed by two independent reviewers utilizing the National Institutes of Health (NIH) Study Quality Assessment Tools. Any disagreements in study selection, data extraction, or quality assessment were adjudicated via discussion between the two reviewers, utilizing a third reviewer as a decider if necessary.

Results: Out of 73 articles identified, there were no duplicates. A total of 73 records were screened, but only 40 articles were assessed in full text for eligibility. A total of 23 articles were ultimately included, which collectively discussed 12,298 participants. Ten (43.5%) of the included studies were cross-sectional in design, three (13.0%) were case reports, and three (13.0%) were retrospective chart reviews. The remaining seven (30.4%) articles were either case-control, cohort, qualitative, controlled observational, or validation studies. Twelve (52.2%) of the studies reported data on depression disorders, six of which reported prevalence data. Nine (39.1%) of the studies reported data on anxiety disorders, five of which reported prevalence data. Studies that reported nonprevalence data presented odds-ratio, mean scores on psychiatric evaluations, and other correlation statistics. Psychiatric disorders that were most reported in these articles were mood disorders (n=11), anxiety disorders (n=9), and neurodevelopmental disorders (n=7). Although the reports varied, the highest psychiatric prevalence reports in EDS patients involved language disorders (63.2%), attention-deficit/hyperactivity disorder (ADHD) (52.4%), anxiety (51.2%), learning disabilities (42.4%), and depression (30.2%).

Conclusions: Although mood disorders were cited in more articles, the highest reported prevalence was for language disorders and ADHD. This discrepancy highlights the importance of performing more research to better understand the relationship between EDS and psychiatric disorders.

Keywords: anxiety; connective tissue disorders; depression; Ehlers-Danlos syndrome; hypermobility; psychiatric disorders; psychology.

Ehlers-Danlos syndromes (EDS) are a group of connective tissue disorders often characterized by joint hypermobility,
skin hyperextensibility, and tissue fragility [1]. EDS are classified into multiple types by their pathophysiology, clinical presentation, and affected tissues. These types have historically been known as classical, hypermobile, vascular, kyphoscoliosis, arthrochalasia, and dermatosparaxis types [1]. The 2017 International Classification of the Ehlers-Danlos syndromes recategorized EDS into 13 standardized types [2]. The prevalence of EDS is estimated to be 1/5,000 individuals with hypermobile EDS (hEDS), representing 80–90% of these cases [3]. An international study from Wales suggested that the prevalence of hEDS is even higher at 1/500 according to the 2017 reclassification [4].

Although primarily characterized by hypermobility, hyperextensibility, and connective tissue defects, the clinical manifestations of EDS are diverse and multidimensional. EDS, specifically the hypermobile subtype, also present with cardiovascular, gastrointestinal, genitourinary, and neurological symptoms that ultimately contribute to a chronic disorder [5]. The experience of chronic pain is associated with subsequent psychopathology and negative emotions [6]. Qualitative interviews with EDS patients revealed that their daily life is burdened by pain, fatigue, social withdrawal, and anxiety regarding their condition [7].

In 1988, researchers at Hospital del Mar in Barcelona first identified a connection between anxiety disorders and EDS [8]. Since then, there has been an increased research focus on the prevalence of anxiety and other psychiatric and psychological conditions among patients with EDS. Psychiatric symptoms, such as depression [8] and panic disorders [9, 10], have been described among EDS and hypermobile patients. Furthermore, a matched cohort study in Sweden identified a significant risk ratio when observing EDS and autism spectrum disorder (ASD), bipolar disorder, depression, suicidal attempts, and attention-deficit/hyperactivity disorder (ADHD) [11]. Researchers in Canada have also described the prevalence of personality disorders, eating disorders, and substance use disorders in a retrospective review of EDS patients [12].

The need for more research and focus on the psychological manifestations of EDS is evident. Patients with EDS could benefit from improved interdisciplinary care, specifically in the psychosocial dimension through counseling on coping strategies and self-efficacy [13].

In this systematic review, we aimed to investigate the prevalence of major psychiatric disorders and psychological manifestations among individuals with EDS. We also present additional statistical measures, including odds ratios, to further understand the nature and extent of the association between EDS and psychiatric disorders. We hypothesize that there is an increased prevalence of psychiatric disorders among the EDS patient population.

To review the existing literature and describe the current state of research into this association. Additionally, we seek to explore the limitations of current studies and ways to improve future studies in an attempt to better understand the relationship between EDS and psychiatric conditions.

Methods

A literature search was conducted utilizing the PubMed database to identify relevant articles published between January 2011 and June 2021 utilizing Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. Figure 1 shows our PRISMA flowchart for study selection. The initial search was performed in June 2021, after which the studies found were imported into the Covidence system. The titles and abstracts were screened for inclusion criteria by three independent reviewers (M.K., K.L., H.G.). Full texts of shortlisted articles were then reviewed to ensure that they met the inclusion criteria by the same reviewers (M.K., K.L., H.G.). Any disputes regarding studies were resolved by independent reviewers during the reconciliation process. Final results were reviewed by the principal investigator (B.R.). Additional relevant articles were included from the bibliography of selected articles found during our database searches.

Search criteria

We included the following search terms: PubMed: (((ehlers danlos syndrome[MeSH Terms]) AND (psychology[MeSH Subheading]) OR (mental disorder[MeSH Terms]))) AND (((2011/01/01[Date - Publication]: “2021/01/01”[Date - Publication]) AND English[Language]): 73 results (23 included).

We limited our search to peer-reviewed journal articles published in the last 10 years. We assessed article quality, study context and design, and outcomes. Inclusion criteria for title and abstract screening included human data, EDS patients, and psychology/psychiatry data meeting our study objective.

Exclusion criteria for title and abstract review involved studies that were not in English, not evidence-based, those that were opinion pieces, conference abstracts, or literature reviews, or those that did not include human subjects or information specific to psychology/psychiatry. This yielded 40 eligible studies for full-text review.

The same inclusion and exclusion criteria were applied during full-text review. In total, 17 full-text studies were rejected for not being evidence-based (n=2), for failing to meet our specific study objective (n=8), and for being review articles and not original research (n=7). This resulted in 23 references for extraction to utilize in our analysis. During the data extraction phase, the quality and risk of publication bias was assessed utilizing the NIH Study Quality Assessment Tools.

Results

Study characteristics

We included 23 studies in our review. The characteristics of these publications are detailed in Table 1. Ten (43.5%) of the included studies were cross-sectional in design, three...
(13.0%) were case reports, and three (13.0%) were retrospective chart reviews. The remaining seven (30.4%) articles were either case-control, cohort, qualitative, controlled observational, or validation studies. Seventeen (73.9%) of the studies were conducted in Europe (France, Italy, Sweden, Belgium, Netherlands, Spain, Switzerland, and Turkey), with the most studies from France (n=5, 21.7%). Only two studies were conducted in, or partially in, the United States. This review aimed to collect primarily prevalence data on psychiatric conditions. Twelve (52.2%) of the included articles presented prevalence data, and the remaining studies presented either odds ratios, risk ratios, correlation measures, or mean and median scores from psychiatric assessments. We present the prevalence data from these studies in Table 2. In Tables 3 and 4, we present prevalence and other reported data on mood and anxiety disorders, respectively. Study quality, internal validity, and risk of bias were assessed utilizing the NIH Study Quality Assessment Tools by two independent reviewers. All 23 included studies were rated as “Good” by reviewers.

**Depression and mood disorders**

The most commonly reported psychiatric conditions in this review were mood disorders. Ten (43.5%) of the included studies reported data relating to mood disorders, most commonly depression. Table 3 displays these studies and their respective findings.

Among these, a retrospective chart review determined a prevalence of 30.2% (n=118) of depression among the EDS and hypermobility spectrum disorder (HSD) cohort of patients (n=391) [15]. When compared to the general Canadian population, the researchers determined the prevalence of depression to be higher among individuals with EDS (95% CI 21.59–43.03, p<0.0001. One study compared Beck Depression Inventory scores between hypermobile patients (n=115) and matched controls (n=114) to reveal a significant mean score difference of 14.57 ± 8.12 vs. 8.37 ± 6.3 in controls, p<0.001 [16]. When comparing the rate of bipolar disorder between patients with EDS (n=1,771) and matched individuals (n=17,710), one nationwide study in Sweden determined a risk ratio of 2.7 (95% CI 1.5–4.7) [17]. Dysthymia (n=2, 4.3%) and minor depressive disorder (n=3, 6.4%) were investigated by one study with 47 cases and 45 controls, but a significant correlation between these disorders and EDS was not determined [18]. The odds ratio for dysthymia and minor depressive disorder utilizing the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) were 2.67 (95% CI 0.23–31.0) and 2.00 (0.31–12.8), respectively [18].
Table 1: Characteristics of included studies.

| Study                  | Title                                                                 | Study type                             | Country      | Investigated phenotype | EDS participants//Total participants |
|------------------------|----------------------------------------------------------------------|----------------------------------------|--------------|-------------------------|--------------------------------------|
| Albayrak et al. (2015) | Is pain the only symptom in patients with benign joint hypermobility syndrome? | Case control study                     | Turkey       | BJHS                    | 115//229                             |
| Baeza-Velasco et al. (2016) | Difficulty eating and significant weight loss in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type | Case report                            | France       | hEDS                    | 2//2                                 |
| Baeza-Velasco et al. (2017) | Cognitive impairment in women with joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type | Controlled observational study         | France       | hEDS                    | 28//49                               |
| Baeza-Velasco et al. (2018) | Low- and high-anxious hypermobile Ehlers-Danlos syndrome patients: Comparison of psychosocial and health variables | Cross-sectional study                  | France       | hEDS                    | 80//80                               |
| Bénistan and Martinez (2019) | Pain in hypermobile Ehlers-Danlos syndrome: New insights using new criteria | Cross-sectional study, qualitative    | France       | hEDS                    | 37//37                               |
| Berglund et al. (2015)  | Self-reported quality of life, anxiety and depression in individuals with Ehlers-Danlos syndrome (EDS): a questionnaire study | Cross-sectional study                  | Sweden       | EDS                     | 250//9,153                           |
| Cederlöf et al. (2016) | Nationwide population-based cohort study of psychiatric disorders in individuals with Ehlers-Danlos syndrome or hypermobility syndrome and their siblings | Cohort study                           | Sweden       | EDS                     | 1,771//19,481                        |
| Celletti et al. (2015) | Phenotypic variability in developmental coordination disorder: clustering of generalized joint hypermobility with attention deficit/hyperactivity disorder, atypical swallowing and narrative difficulties | Cross-sectional study                  | Italy and US | gJHM                    | 19//41                               |
| Cravero et al. (2016)  | Cornelia de Lange and Ehlers-Danlos: Co-morbidity of two rare syndromes | Case report                            | France       | EDS                     | 1//1                                 |
| De Wandele et al. (2014) | Autonomic symptom burden in the hypermobility type of Ehlers-Danlos syndrome: a comparative study with two other EDS types, fibromyalgia, and healthy controls | Cross-sectional study                  | Belgium      | hEDS, cEDS, vEDS        | 98//179                              |
| Domany et al. (2018)   | Sleep Disorders and their management in children with Ehlers-Danlos syndrome referred to sleep clinics | Retrospective chart review             | United States | EDS                     | 65//65                               |
| Gaisl et al. (2017)    | Obstructive sleep apnoea and quality of life in Ehlers-Danlos syndrome: a Parallel cohort study | Cohort study                           | Switzerland  | EDS                     | 100//200                             |
| Hershenfeld et al. (2016) | Psychiatric disorders in Ehlers-Danlos syndrome are frequent, diverse and strongly associated with pain | Retrospective chart review             | Canada       | hEDS, cEDS              | 106//106                             |
| Krahe et al. (2018)    | Features that exacerbate fatigue severity in joint hypermobility syndrome/Ehlers-Danlos syndrome – hypermobility type | Cross-sectional study                  | Australia    | hEDS                    | 117//117                             |
| Lee and Strand (2018)  | Ehlers-Danlos syndrome in a young woman with anorexia nervosa and complex somatic symptoms | Case report                            | Sweden       | EDS                     | 1//1                                 |
| Morlino et al. (2019)  | Italian validation of the functional difficulties questionnaire (FDQ-9) and its correlation with major determinants of quality of life in adults with hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorder | Validation study                       | Italy        | hEDS, HSD               | 105//210                             |
| Nicholson et al. (2017) | Physical and psychosocial characteristics of current child dancers and nondancers with Systemic joint hypermobility: a descriptive analysis | Cross-sectional study                  | Australia    | hEDS                    | 102//102                             |
Anxiety disorders

Anxiety disorders (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder) were frequently studied by the publications included in this review. Most commonly, the studies reported data on nonspecific anxiety, combining generalized anxiety disorder with other anxiety disorders. Eight (34.8%) studies described anxiety disorders among EDS patients. Findings from these studies are reported in Table 4.

The reported prevalence of anxiety in EDS individuals ranged widely with several different diagnostic tools being utilized. Anxiety was reported by 85 (9.0%) individuals with EDS (n=946) utilizing a self-reporting questionnaire [19]. Other researchers, utilizing the Hospital Anxiety and Depression Scale (HADS), observed 41 patients (51.2%) with anxiety among the EDS patient population (n=80) [20]. A retrospective chart review found that anxiety disorders were more common among EDS patients (n=104, 26.6%) than the general Canadian population (95% CI 22.74–44.39, p<0.0001) [15]. However, another article, describing the results of a case-control study (n=47 cases, 45 controls), found insignificant relationships between the two, with odds ratios of 3.13 (95% CI 0.92–10.7, p=0.07) and 0.19 (95% CI 0.01–3.82) utilizing the HAM-A and SCID-1, respectively [18].

Neurodevelopmental disorders

Neurodevelopmental disorders, such as ADHD, ASD, learning disabilities, and language disorders, were studied in seven (30.4%) of the included publications.

ADHD was most frequently investigated, with prevalence reports ranging from 4.6% (n=18, total EDS n=79) [21] to 52.4% (n=55, total EDS n=105) [22]. A nationwide study in Sweden reported a risk ratio for ADHD of 2.1 (95% CI 1.4–3.3) between EDS patients (n=1,722) and their siblings (n=16,920), and 5.6 (95% CI 4.2–7.4) between HSD patients (n=10,019) and matched subjects (n=100,190). The same study reported a significant risk ratio for ASD of 7.4 (95% CI 5.2–10.7) between HSD patients and matched subjects. However, when comparing EDS patients and
### Table 2: Psychiatric prevalence data.

| Disorder                                      | Alpayrak et al. (2015) | Baeza-Velasco et al. (2018) | Bénistan and et al. (2016) | Cederlöf et al. (2015) | Domany et al. (2018) | Gaisl et al. (2017) | Hershenfeld et al. (2016) | Morlino et al. (2019) | Pasquini et al. (2014) | Simmonds et al. (2019) | Wasim et al. (2019) |
|------------------------------------------------|------------------------|-------------------------------|-----------------------------|------------------------|----------------------|------------------------|---------------------------|------------------------|-------------------------|-----------------------|---------------------|
| Depression, NOS                                | 51 (44.3)              | 16 (20.0)                     | 8 (21.6)                    | 72 (4.2)               | 27 (25.5)            | 4 (8.5)                | 259 (27.4)                 | 118 (2.0)               | 104 (2.6)                | 85 (9.0)               | 3 (0.3)              |
| Anxiety, NOS                                    | 41 (51.3)              | 3 (7.5)                       | 17 (89.5)                   | 55 (52.4)              | 18 (9.3)             | 11 (23.4)              | 85 (9.0)                   | 104 (2.6)               | 7 (1.9)                  | 54 (5.7)              |                     |
| Attention deficit disorder with hyperactivity   | 26 (1.5)               | 17 (89.5)                     | 7 (6.6)                     | 55 (52.4)              | 18 (9.3)             | 11 (23.4)              | 85 (9.0)                   | 104 (2.6)               | 7 (1.9)                  | 54 (5.7)              |                     |
| Bipolar disorder                               | 7 (0.5)                | 2 (1.9)                       | 7 (1.9)                     |                       |                      |                       |                           |                         |                         |                       |                     |
| Mental health condition, NOS                   | 10 (0.6)               | 9 (47.4)                      | 2 (1.9)                     |                       |                      |                       |                           |                         |                         |                       |                     |
| Learning difficulties                          |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Fatigue                                        | 36 (97.3)              |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Suicide attempt                                | 8 (21.6)               | 66 (3.8)                      | 2 (0.5)                     |                       |                      |                       |                           |                         |                         |                       |                     |
| Autism spectrum disorder                       |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Obsessive compulsive disorder                  |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Panic disorder                                 |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Adjustment disorder                            |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Schizophrenia                                  |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Schizoaffective disorder                       |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Anorexia nervosa                               |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Bulimia                                        |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Conduct disorder                               |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Dysthymic disorder                             |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Histrionic personality disorder                |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Minor depression                               |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Borderline personality disorder                |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Narcissistic personality disorder              |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |
| Schizoid personality disorder                  |                        |                               |                             |                       |                      |                       |                           |                         |                         |                       |                     |

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siblings, the reported risk ratio for ASD was not significant at 1.8 (95% CI 0.9–3.4) [17]. Learning disabilities (n=9, 47.4%, p=0.184) and language disorders (n=12, 63.2%, p=0.518) were found to be more prevalent among hypermobile patients (n=19), but a significant correlation could not be determined [22].

### Personality disorders

Three papers investigated the occurrence of personality disorders among EDS patients. Obsessive compulsive, narcissistic, and schizoid personality disorders were found to be more prevalent among EDS patients (n=47) than controls (n=45) with odds ratios of 12.8 (95% CI 0.68–238.4), 3.48 (95% CI 0.14–88.0), and 5.80 (95% CI 0.27–124.6), respectively [18]. The prevalence of schizotypal personality disorder in EDS patients was reported in two studies as 0.3% (n=1, total n=79) [15] and 0.9% (n=1, total n=106) [12].

### Miscellaneous psychiatric disorders

Table 2 reports the prevalence data extracted from the included studies. Over 70 psychiatric disorders were...
Table 3: Mood disorders.

| Study                      | EDS participants/Total participants | Diagnostic tool                  | Depression, NOS | Major depressive disorder | Mood disorders, NOS | Bipolar disorder | Dysthymic disorder | Minor depressive disorder |
|----------------------------|-------------------------------------|-----------------------------------|----------------|--------------------------|--------------------|-----------------|---------------------|--------------------------|
| Albayrak et al. (2015)     | 115/229                             | Beck depression index             |                | Mean score 14.57 ± 8.12  vs. 8.37 ± 6.3 controls p<0.001 |
| Baeza-Velasco et al. (2018)| 80/80                               | Self-reported                     |                | Prevalence n=16, 20.0%   |
| Bénistan and Martinez      | 37/37                               | HAD-D questionnaire               |                | Prevalence n=8, 21.6%    |
| Berglund et al. (2015)     | 250/9,153                           | HAD-D questionnaire               |                | Mean score 9.1, (CI 8.9–9.4)   |
| Cederlöf et al. (2016)     | 1,771/19,481                        | Diagnosed by medical professionals| Prevalence n=76, 4.3% | Risk ratio EDS vs. matched: 3.4 (CI 2.9–4.1) |
| Hershnenfeld et al. (2016) | 106/106                             | Diagnosed by medical professionals| Prevalence n=27, 25.5% |                |
| Krahe et al. (2018)        | 117/117                             | DASS-21                           |                | Prevalence n=15, 0.9%    Risk ratio EDS vs. matched: 2.7 (CI 1.5–4.7) |
| Pasquini et al. (2014)     | 47/92                               | HAM-D SCID-1                      | Mean score 10/42 (8.7) | Prevalence SCID-1: n=4, 8.5% Odds ratio SCID-1 all: 11.9 (CI 0.62–231.3) |
| Simmonds et al. (2019)     | 946/946                             | Self-reported                     |                | Prevalence n=259, 27.4%  |
| Wasim et al. (2019)        | 79/391                              | Diagnosed by medical professionals| Prevalence n=118, 30.2% | Prevalence n=135, 34.5% |

CI, confidence interval; DASS-21, Depression anxiety stress scale-21; EDS, Ehlers-Danlos syndrome; HAD-D, Depression component of the Hospital Anxiety and Depression Scale (HADS); HAM-D, Hamilton rating scale for depression; NOS, not otherwise specified; SCID-1, structured clinical interview for DSM-IV for axis-1 disorders.

Examined by the included studies, but some studies only provided other measures outside the initial scope of this systematic review. The following findings, although not reported as prevalence data, further depict the correlations between psychiatric disorders and EDS.

Patients with EDS (n=115) scored higher for sleep quality disorders than healthy controls with a mean score of 7.53 ± 2.86 vs. 6.14 ± 2.96 controls (n=114), p<0.001 [16]. Risk ratios of 1.8 (95% CI 1.4–2.3) between EDS patients (n=1,722) and siblings (n=16,920) and 2.1 (95% CI 1.7–2.7) between EDS patients and controls (n=114).
between EDS patients (n=10,019) and matched subjects (n=100,190) were reported for suicide attempt [17].

**Discussion**

Prevalence reporting in any review may vary based on the design of each individual study. In studies evaluating psychiatric and psychological conditions, this difficulty is compounded by the sometimes subjective nature of symptoms and their evaluation. While certain psychological conditions were noted to have higher prevalence than others in EDS patients, it should be highlighted that there was often a wide range between reported prevalence values, which highlights how variability in study methodology and the nuances of similar diagnoses and their diagnostic criteria may alter perceptions of how prevalent certain conditions are. For example, while EDS patient depression prevalence was in one report stated to be as high as 30.2% [16], it was reported as low as 11.1% in EDS patients in another study [17]. In a similar way, anxiety was reported as high as 51.2% [20] in one study but as low as 9.0% [19] in another study; of note, these two studies utilized different reporting scales, but counterintuitively, the self-reporting scale was associated with prevalence on the lower end of the spectrum. ADHD prevalence reports were found to range from 4.6% [15] to 52.4% [22]; again counterintuitively, the higher number correlated with DSM-IV criteria and the lower end of the range corresponded to a study that utilized self-reports associated with prevalence on the lower end of the spectrum.

Krahe et al. [22], but they were not mentioned in the other articles we reviewed. Additionally, it should be noted that this was categorized as “language disorders, not otherwise specified,” which is inherently a vague label and may explain in part the high prevalence value.

The variability in prevalence reporting does pose the question of whether the reported prevalence of psychiatric conditions in EDS is significant due to the underlying disease process or rather just a coincidence. However, these values, even at their lower ends, are in some cases higher than the reported prevalence of the same conditions in the general population. For example, adult ADHD prevalence has been estimated to be between 2.5 and 4% [23]. One study evaluating depression in European countries found it to be 6.4% (95% CI 6.24–6.52) [24]. Among Europeans ages

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**Table 4: Anxiety disorders.**

| Study                        | EDS participants// | Diagnostic tool | Anxiety, NOS | Panic disorder | Obsessive compulsive disorder |
|------------------------------|-------------------|-----------------|--------------|----------------|-------------------------------|
| Baeza-Velasco et al. (2018)  | 80//80            | HADS            | Prevalence   | Prevalence n=41, 51.2% | Odds ratio SCID-1: 1.33 (CI 0.18–10.1) |
| Bénistan and Martinez (2019) | 37//37            | HADS            | Mean score   | Prevalence n=3, 7.5% |                                |
| Berglund et al. (2015)       | 250//9,153        | HADS            | Mean score   | 12.0, (CI 11.7–12.4) |                                |
| Hershenfeld et al. (2016)    | 106//106          | Diagnosed by medical professionals | Prevalence n=25, 23.6% |                                |                                |
| Krahe et al. (2018)          | 117//117          | DASS-42         | Mean score   | 9.35/42 (7.2) |                                |
| Pasquini et al. (2014)       | 47//92            | HAM-A SCID-1    | Prevalence SCID-1: n=0 (0.0%) | Odds ratio HAM-A: 6.7 vs. 3.8 controls, p=0.008 (CI 0.01–3.82) |
| Simmonds et al. (2019)       | 946//946          | Self-reported   | Prevalence n=85, 9.0% |                                | Prevalence n=13, 1.3% |
| Wasim et al. (2019)          | 79//391           | Diagnosed by medical professionals | Prevalence n=104, 26.6% |                                |                                |

CI, confidence EDS, Ehlers-Danlos syndrome; HADS, hospital anxiety and depression scale; HAM-A, Hamilton rating scale for anxiety; NOS, not otherwise specified; SCID-1, structured clinical interview for DSM-IV for axis-1 disorders.
14 to 65, the prevalence of anxiety disorders has been cited to be as high as 14% [25], which is slightly higher than the lower end of the reported prevalence spectrum for EDS and suggests that there might not be much of a difference in anxiety between EDS patients and the general population. Language disorder prevalence values have been reported to be between 3 and 8% [26].

While the increased prevalence of anxiety and depression in connective tissue disorders like EDS is relatively intuitive, the increased prevalence of language disorders is not as obvious. Only one of the articles we reviewed specifically studied language disorders, so the high prevalence may not be as high on repeat evaluations. However, language disorders can be related to vocal cord abnormalities due to underlying collagen [22, 27], which might explain the increased prevalence in these patients.

It is critical to provide evidence for the psychiatric manifestations of EDS in order to better support patients. EDS patients already face enough hardship in the diagnostic process, which can take up to 20 years [20]. This difficulty is compounded by how patients can feel “misunderstood and judged” by healthcare providers [28].

Additionally, the burden of pain that these patients experience may play a role in the psychological manifestations of disease. One study found a positive relationship between having pain (e.g., joint pain or abdominal pain) and any psychiatric disorder, as measured by odds ratio [12]. Fear of pain associated with, for example, eating-related oral/abdominal pain and with movement can accumulate over the disease course in EDS patients and result in anxiety in these patients [29].

One study suggested that enhanced awareness of body positioning and central sensitization is related to the mental health of these patients; this is mediated by “long-term changes in the nervous system,” specifically “synaptic plasticity” and/or “continuous stimulation of peripheral nociceptors by mediators released from the aberrant extracellular matrix” [19].

From the perspective of osteopathic medicine, the person is valued as a unit of mind, body, and spirit. Our team, composed of three osteopathic medical students and an osteopathic physician, is particularly focused on how this tenet relates to the psychiatric morbidity observed in EDS. Further, the need for an osteopathic perspective on psychiatry would address the physical experience of pain in musculoskeletal disorders and the burdens of psychological distress [30]. The mediating neuromechanical processes hypothesized in EDS could be a focus of future research on the role of osteopathic manipulative treatment (OMT) in this patient population [21]. Postural orthostatic tachycardia syndrome (POTS) has been associated with EDS as a concurrent diagnosis [31]. OMT was described as a successful intervention in the case report of a 26-year-old woman with POTS [32]. Their work highlighted the potential of rib raising, suboccipital decompression, and cranial manipulation as a method to stabilize the autonomic nervous system [33–35]. Utilizing the framework that these researchers described, treatments of the autonomic nervous system should be considered for patients experiencing anxiety comorbid to EDS. Currently, the intersection of EDS and OMT is not well studied, so there is room for more scientific exploration on this matter.

Limitations of this study included the relatively small sample size. We ultimately analyzed 23 articles that described a total of 4,190 EDS patients. Prevalence reports of EDS vary, ranging from 1 [28] to 10 [5] cases per 5,000 people. Considering the billions of people in the world, and those that are undiagnosed with EDS/joint hypermobility syndrome (JHS) and its psychiatric diagnoses, we are likely underestimating the prevalence of the psychiatric manifestations in EDS. Another limitation of this study is the subjective nature of identifying psychiatric symptoms. Self-assessment–based questionnaires were a frequently utilized tool in the reviewed studies, which opens up this review to potential bias.

Future research of the psychological manifestations of EDS could involve a prospective study of EDS patients from time of diagnosis. Prevalence could be calculated separately for male and female patients to correct for any bias related to the increased frequencies of certain conditions in different sexes. Additionally, data could be collected on siblings to evaluate the effects of confounding variables such as familial disposition vs. disease position.

Conclusions

As described in this review, the past 10 years have fostered increasing focus on the psychiatric manifestations of EDS. There are, however, gaps in the existing literature that would better our understanding of this clinical relationship. The variations in data, confounded by nonuniform methodology, prevent us from confirming the hypothesis that psychiatric disorders are more prevalent among individuals with EDS. The use of standardized evaluation tools, sibling studies, and uniform reporting practices in future studies would allow researchers to draw stronger and definitive conclusions regarding the association between psychiatric conditions and EDS. Thus, more
research is needed to improve preventative and therapeutic measures while caring for EDS patients and to better address the comorbidities of their disease.

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