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Health-Related Quality of Life among Adult Patients with Ehlers-Danlos Syndrome: A Systematic Review and Meta-Analysis

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Abstract

Background: Ehlers-Danlos Syndrome (EDS) is a serious chronic condition that leads to diminished quality of life and psychological problems. The current study aimed to systematically reviewed the existing literature on EDS patients' health-related quality of life (HRQoL), calculate mean HRQoL value, and determine the association between demographical and publication-related characteristics with HRQoL.

Methods: Four electronic databases were used to identify papers on HRQOL in adults with EDS (Scopus, Medline (by Pubmed), Epistemonikos, and Web of Science). A random-effects meta-analysis was also performed on the 36-item Short Form Survey (SF-36) measure.

Results: We contained 37 studies that fulfilled the inclusion criteria. According to the SF-36 meta-analysis, EDS patients and the general population had significant differences in all HRQoL components ($p<0.01$). In EDS patients, the Physical Component Summary (35.34/100) was more seriously impacted than the Mental Component Summary (45.21/100) in these patients.

Conclusion: Individuals with EDS have significantly lower HRQoL in all aspects compared to the general population, with the physical component of wellbeing being the most pronounced disparity. Future research should look into the impact of different patient characteristics, evaluate the complications of EDS and their effects on wellbeing, and develop multiple intervention strategies to improve HRQoL.

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1. Introduction

Ehlers-Danlos Syndrome (EDS) is a group of inherited disorders caused by the defect in collagen production. It can be divided into six types (i.e., classical, hypermobility, vascular, kyphoscoliotic, arthrochalasia, and dermatosparaxis) based on genetic characteristics and clinical manifestations (Albayrak et al., 2015). The manifestations vary from mild type (bruising and elastic stretchy skin) to life-threatening, such as vascular rupture (Velasco et al., 2018). The disease's main characteristics include joint hypermobility, skin hyperextensibility, tissue fragility, and easy bruising (Sobey, 2014).

The hypermobility type is the most common EDS variant (80-90% of all cases), with a prevalence of 1 in 5000, and is associated with chronic joint and limb pain (Arthur et al., 2016; Tinkle et al., 2017). However, it is frequently underdiagnosed, as a study completed in Wales, UK, demonstrated a prevalence of 10 cases per 5000 individuals, much higher than commonly reported estimate number (Demmler et al., 2019). Determination of hypermobility type EDS can be done with a standardized criterion, named Beighton criteria, which has 5/9 cut-off for diagnosis establishment (Smits-Engelsman et al., 2011). Patients affected by this EDS type have a diminished joint position sense, which may render the joint more susceptible to injury, subluxation, and dislocation (Tinkle et al., 2017). Bowel problems, poor wound healing, food hypersensitivities, muscle cramps, and adverse pregnancy outcomes are some other clinical features that can present among EDS patients (Berglund & Björck, 2012). Furthermore, chronic pain can lead to disability in addition to deleterious impact on sleep quality and quality of life (QoL), which can result in a dysfunctional (high distress, sensitivity, and terrible pain) or highly dysfunctional and distressed profile (remarkably high distress, sensitivity, and devastating pain) (Gana et al., 2021). Following this disturbance, numerous psychiatric problems such as depression, anxiety, panic disorder, and phobia may develop (Albayrak et al., 2015).

Health-related quality of life (HRQoL) is an approach used to investigate the impact of specific health status on human wellbeing (Caruso et al., 2014; Yin et al., 2016). It can be assessed using validated screening instruments, such as the 36-Item Short Form Survey (SF-36), 12-Item Short-Form Health Survey (SF-12), and World Health Organization Quality of Life (WHOQoL) or newly developed questionnaires (Caruso et al., 2014; Pequeno et al., 2020). Data acquisition can be done either through the self-administered or the interview methods. It is an essential component to be assessed in patient management, especially in genetic and chronic diseases (Adjei et al., 2021; Caruso et al., 2014; Vita et al., 2020).

EDS is a lifelong disabling disease, restricting almost every aspect of the patients' lifestyles (Berglund et al., 2015). This is evidenced by the finding of most studies, which consistently report that EDS is associated with poor QoL and psychiatric disorders (Orenius et al., 2022). This is related with several events associated with the disease (hypotonia, respiratory problem, low sleep quality, dysautonomia, gut malabsorption, and psychiatric disorder) or medication (mainly inappropriate use of analgesics) (Castori, 2012). Consequently, the assessment of the QoL among EDS patients is one of the most important aspects of exploring the underlying impacts of living with EDS, investigating their needs, and deciding crucial steps for the prevention of personal worsening (Berglund et al., 2015). The assessment of QoL in this particular type of patient requires a multidisciplinary approach (Bovet et al., 2016; Rocchetti et al., 2021). Therefore, the present study systematically reviewed the available literature on HRQoL in patients with EDS, determine mean HRQoL value, and verify the association between observed demographical and publication-related characteristics with HRQoL.

2. Materials and Methods

An extensive systematic literature review utilizing multiple databases was conducted to explore scientific articles about the HRQoL among EDS patients. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 recommendations (Page et al., 2021) were used to construct this review. Before the literature search was conducted, all working group participants endorsed the study procedure. This systematic review's study protocol was registered to the International Prospective Registry of Systematic Reviews (PROSPERO) database (www.crd.york.ac.uk/prospero/) (PROSPERO ID: CRD42022326217).

2.1 Eligibility criteria

This review targeted publications about adult patients diagnosed with EDS (using any recognized diagnostic criteria) employed from the general community, primary care, or secondary care facilities. We included observational investigations (prospective or retrospective cohort, case-control, or cross-sectional study) and experimental studies (randomized controlled trials, pre-post-test, or quasi-experimental research) that used a validated HRQoL questionnaire. Conference abstracts, editorials, letters to the editor, literature reviews, protocols, correspondence, perspectives, opinions, posters, case reports, and/or case series were excluded from the consideration. Only full-text manuscripts published in English were included to guarantee data precision.

2.2 Search strategy

The search (completed in April 2022) was conducted electronically in four different databases: *Scopus* (626 hits), *Medline* (via *Pubmed*) (443 hits), *Epistemonikos* (382 hits), and *Web of Science* (83 hits). The following search terms were incorporated into the search strategy: ("quality of life"

OR "QOL" OR "health-related quality of life" OR "HRQOL" OR "wellbeing" OR "psychological wellbeing" OR "wellness" OR "health perception" OR "health satisfaction" OR "health status" OR "Quality of Life assessment") AND ("Ehlers Danlos Syndrome" OR "Ehlers-Danlos Syndrome" OR "Cutis Elastica" OR "EDS") AND ("adult" OR "young adult" OR "middle-aged"). The studies found through the database search were evaluated based on their titles and abstracts, and only those that met the eligibility criteria were considered for further analysis. There were no time restrictions on the retrieved studies. In addition, handsearching of the reference lists (n = 38) was also performed to gather any additional studies.

2.3 Study selection

The retrieved papers were inspected for potential duplication. Two independent reviewers (MAM and MC) used *Rayyan QCRI*, a semi-automated abstract and title sorting program, to screen the titles and abstracts (Ouzzani et al., 2016; Umar et al., 2022). Inter-rater disagreements were resolved by careful re-examination and consultation of the paper among reviewers until a consensus was attained. The full texts of potentially eligible studies were acquired and independently evaluated by two reviewers (RS and TPU) to determine eligibility for inclusion in the final analysis. The full-text screening stage used a similar method of resolving the disagreements among researchers. If no settlement could be actualized, a moderator (LM) was present to re-evaluated the distinctions and finalized the manuscript inclusion designation.

2.4 Data extraction

The primary data extraction was done by MC, HS, and RM. The following information was extracted: authorship, year and country where the study took place, study types, sample size (male/female), QoL assessment instrument, and main findings. Two of the co-authors (RS and TPU) independently assessed the risk of bias in the included studies, with contradictions resolved through deliberation among researchers until a conclusion was reached. The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to critically evaluate and analyse the methodological quality of each study. The NOS is divided into three sections: selection, comparability, and outcome. It is evaluated using a star system, with up to nine stars (or ten stars for cross-sectional research) awarded across the three domains (Liana et al., 2022).

2.5 Statistical analysis

After compiling all of the included studies, the data were entered into Microsoft Excel 2019 (version 2102). The Kappa-Cohen test ($\varkappa$) was measured for both the abstract screening and full-text examination stages to assess inter-rater agreement. The following values were predetermined to indicate the definition of agreement: 0.01–0.20, none to slight agreement;

0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.00, nearly perfect agreement (McHugh, 2012). Correlation analysis was also performed using Pearson's correlation coefficient or Spearman's rank correlation coefficient, based on the data distribution to assess the association between several observed variables in the included studies (specified in the results section). *IBM SPSS Statistics for Windows*, Version 26.0, was used for statistical analysis (Armonk, New York: IBM Corp., 2019).

Due to the high level of heterogeneity found across various studies (as determined using I2-values >50%) (Higgins et al., 2003), random-effects meta-analysis were conducted using *Review Manager (RevMan)* Version 5.4.1. (Copenhagen: The Cochrane Collaboration, 2020). Meta-analysis was carried out for each domain of the 36-Item Short Form Survey (SF-36) (Tadrous et al., 2021). In order for studies to be eligible for inclusion in the meta-analysis, they were required to report mean scores and standard deviations (SDs) for each participant. However, if the central tendency was presented as a median or the data dispersion as a 95% CI or range, it was converted using the Wan et al. formula (Wan et al., 2014). Differences between EDS and the general population group value of SF-36 were presented in mean difference (MD). In the meta-analysis, all p-values were two-sided, and $p<0.05$ was considered significant.

2.6 Publication bias

Publication bias was examined by funnel plots, Begg and Mazumdar rank correlation test, and Egger's linear regression test with *RevMan Version 5.4.1* (Copenhagen: The Cochrane Collaboration, 2020) and *Comprehensive Meta-Analysis Version 3.3* (Englewood, New Jersey: Biostat, 2014). An asymmetric distribution of datasets in the funnel plot and a quantified result of $p<0.05$ in the Begg's and Egger's tests demonstrated possible publication bias. Other than publication bias, asymmetry in the funnel plot was influenced by minor study effects, heterogeneity, and odds, especially in small sample-size studies. To investigate the stability of the outcome, sensitivity analysis was conducted by removing each record incrementally.

2.7 Meta-regression

Meta-regressions were performed on all SF-36 variables, including Physical Functioning (PF), Physical Role Limitations (RP), Bodily Pain (BP), General Health (GH), Physical Component Summary (PCS), Vitality (V), Social Functioning (SF), Emotional Role Limitations (RE), Mental Health (MH), and Mental Component Summary (MCS) due to statistically significant and substantial heterogeneity (I2) and fulfilling the minimum required studies (≥10) threshold. Meta-regression was used to permit the integration of more than one covariate. Our meta-regression included three covariates: publication year, male/female ratio, and participant age. In a random-effects meta-regression model, these covariates were meta-regressed separately and together using *Comprehensive Meta-Analysis Version 3.3* (Englewood, New Jersey: Biostat, 2014).

3. Results

3.1 Characteristics of included studies

The search strategy yielded 1572 papers. After removing 489 duplicates, 1083 unique papers had their titles and abstracts assessed for eligibility checking. In the final phase, 37 studies met the inclusion requirements. There is a substantial inter-rater agreement with 97.7% and 89.8% of agreement in the first and second screening phase, respectively ($\varkappa = 0.707$, $p<0.001$). From the 37 papers included in the descriptive synthesis, ten studies were included in the SF-36 meta-analysis. The PRISMA flow diagram, which depicts the study selection process and the reasons for exclusion, is presented in Figure 1.

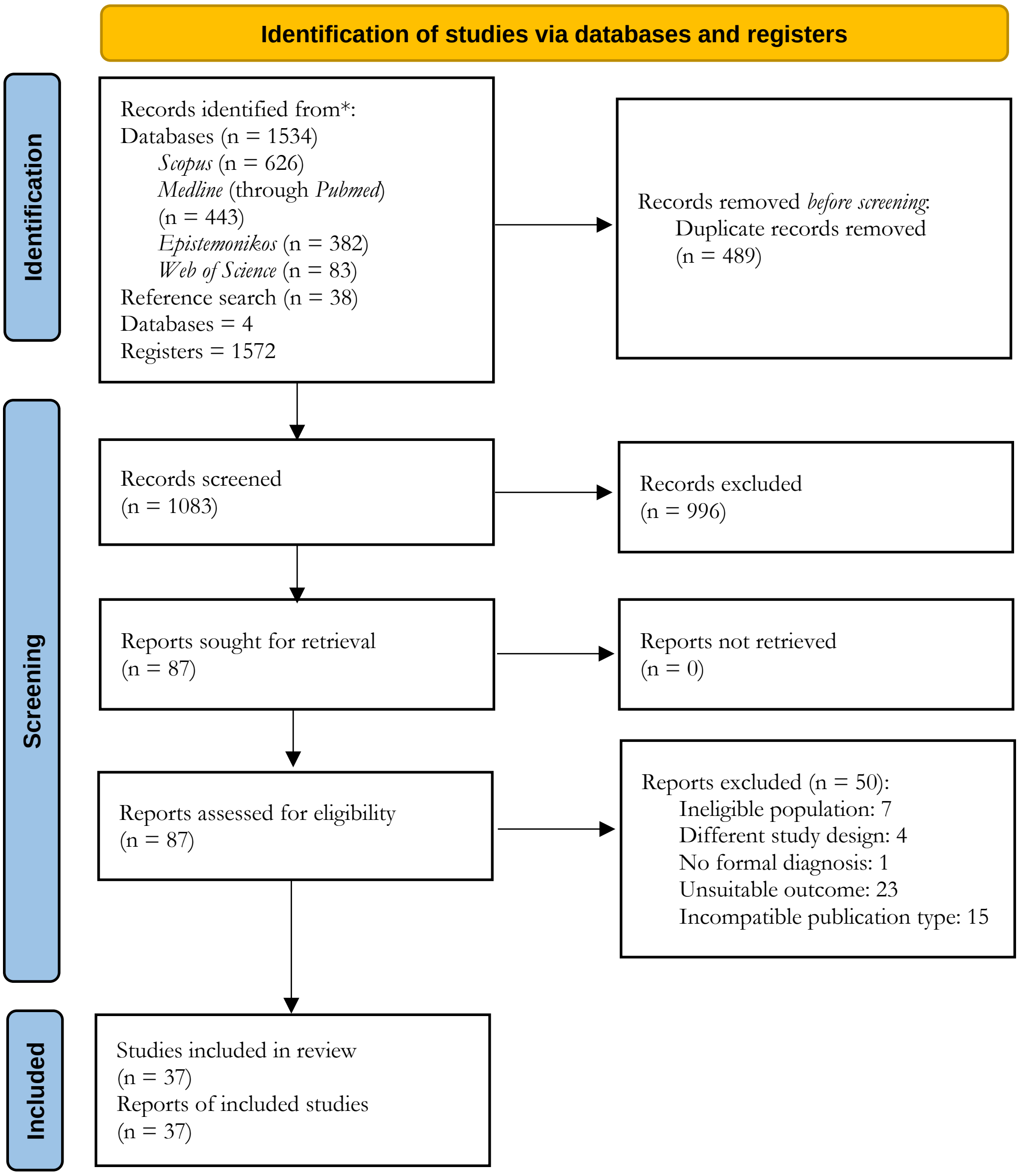

Figure 1. PRISMA flow diagram

The majority of these studies (31 of 37; 83.78%) were cross-sectional studies, with a total of 8251 EDS patients, all of whom were adults (older than 18 years), predominantly female (n=7541; 91.39%), and diagnosed with EDS using Beighton criteria, Villefranche criteria, or self-report (based on physician examination). Nineteen studies compared EDS patients to the general population, nine papers compared EDS patients to other chronic diseases such as rheumatoid arthritis, fibromyalgia, gastrointestinal disorder, Marfan syndrome, or migraine, and nine studies had no comparison group. Thirteen studies reported the proportion of EDS-HT (hypermobility type) as the most common types of EDS (2570/4271; 60.17%). Ten studies (Albayrak et al., 2015; Bénistan & Martinez, 2019; Celletti et al., 2013; Johannessen et al., 2016; Molander et al., 2020; Palomo-Toucedo et al., 2020; Puledda et al., 2015; Rombaut et al., 2010; Rombaut, Malfait, De Wandele, et al., 2011; Voermans et al., 2010) reported pain levels (using numeric rating scale), with an average score of 6.23/10. Furthermore, the Beighton score was present in eight studies (Albayrak et al., 2015; Celletti et al., 2013; Gaisl et al., 2017; Jeffery et al., 2021; Krahe et al., 2018; Martinez et al., 2021; Morlino et al., 2019; Rombaut et al., 2010), with a mean score of 6.15/9 (following the 5/9 thresholds). Table 1 summarizes the key characteristics of the included studies.

Table 1. Summary of included studies

Author (year)	Country	Study type	Sample size	Male/ Female	Age (years) **	BMI (kg/m²)	Diagnostic procedure	QoL Instrument	Comparison group	Quality score	Main findings	EDS-HT propor-tion	Pain assessment method	Beighton score (max. 9)
(Albayrak et al., 2015)	Turkey	Cross-sectional	115	13/102	30.17± 7.47	25.21± 5.02	Brighton Criteria	SF-36	Matched healthy controls	6/10	SF-36 subscales among EDS patient was significantly lower than the control group.	N/A	VAS (NRS)	6.73
(Arthur et al., 2016)	USA	Cross-sectional	1179	60/1107*	37.78± 12.21	N/A	Self-reported	Neuro-QOL	Normal population	7/10	Patients with EDS had higher levels of pain interference and lower satisfaction with social roles and activities than the general population. The most common modalities for treating pain among EDS patients were opioids, surgical interventions, splints and braces, avoidance of potentially dangerous activities, heat therapy, and massage therapies.	885/1107	PROMIS-PI PROMIS-PB	N/A
(Berglund & Björck, 2012)	Sweden	Cross-sectional	250	27/223	46,1±12	N/A	1997 diagnostic criteria	OHIP-14	Normal population	5/10	Women with EDS had a lower oral health-related QoL as measured with the OHIP-14.	76/250	N/A	N/A
(Berglund & Nordström, 2001)	Sweden	Cross-sectional	77	8/69	39 (18–70)	N/A	Beighton criteria	SIP	Normal population, females with rheumatoid arthritis, and females with fibromyalgia	5/10	EDS patients had worse functional health status in all SIP subscales when compared to the general population. Women with EDS had better functional health than women with rheumatoid arthritis. In comparison to fibromyalgia patients, female EDS patients rated their functional health status as worse on the physical dimension and home management subscale, but better on the work subscale.	23/77	N/A	N/A
(Berglund et al., 2015)	Sweden	Cross-sectional	250	27/223	46.1 (44.5-47.7)	25.8 (25.1-26.5)	Beighton criteria	SF-36	Normal population	5/10	In comparison to the general population, the EDS group had a lower health-related quality of life (as shown by the SF-36 value). Individuals with EDS had higher levels of anxiety and depression.	76/250	Back pain variable	N/A

(Bénistan & Martinez, 2019)	France	Cohort	37	1/36	26 ± 10	23 ± 4	2017 International Classification Criteria	BPI	No control group	2/9	EDS patients who presented with generalized pain had longer period of chronic pain and a greater impact on the affective component.	N/A	NRS	N/A
(Bovet et al., 2016)	USA	Cross-sectional	38	6/32	36 (19–64)	24.6	Self-reported	SF-36	Normal population	6/10	EDS patients had poor HRQoL with 71% reporting worse health over the past year. SF-36 scores among EDS patients were significantly lower than the average American population.	N/A	N/A	N/A
(Celletti et al., 2013)	Italy	Cross-sectional	42	2/40	32.80 ± 13.23	N/A	Brighton criteria and Villefranche criteria	SF-36	Normal population	6/10	Kinesiophobia was a common JHS/EDS-HT symptom. In the EDS group, there was a marked reduction in QoL, moderate/severe bodily pain, and significant fatigue.	N/A	NRS	5.47
(Demes et al., 2020)	Multi-country	Cohort	486	24/462	37.4	N/A	Self-reported	SF-36	Normal population	8/9	EDS patients had lower SF-36 scores in all domains when compared to the general Norwegian population. The majority of participants reported that their worst pain in the previous seven days was severe and that it interfered with their enjoyment of life.	195/486	Baseline pain score (average pain rating)	N/A
(De Wandele et al., 2014)	Belgium	Cross-sectional	98	12/86	39.51 ± 12.21	23.79 ± 4.37	Villefranche criteria	SF-36	Normal population and fibromyalgia patients	6/10	Autonomic symptoms, especially orthostatic and gastrointestinal complaints, contributed to the disease burden in EDS-HT. These symptoms were related to a lowered quality of life and to an increased fatigue and pain severity.	80/98	PDQ	N/A
(Fikree et al., 2015)	UK	Case-control	336	116/220	42 (40.9–43.1)	N/A	Brighton criteria	SF-36	Organic gastro-intestinal disorder patients	7/9	EDS patients had significant association with the occurrence of functional gastrointestinal disorders (FGID), and this subgroup of patients had increased comorbidity and decreased QoL.	N/A	N/A	N/A
(Fikree et al., 2017)	UK	Cross-sectional	74	26/48	21.0 (18–35)	22.04	Villefranche criteria	SF-36	Normal population and fibromyalgia patients	4/10	Students with EDS-HT scored less on the SF-36's pain subscale than the general population. There were no differences in the emotional, social, or physical domains.	N/A	N/A	N/A
(Gaisl et al., 2017)	Switzer-land	Cohort	100	18/82	39.9± 12.8	24.4±5.6	Beighton criteria	SF-36	Matched healthy controls	7/9	OSA was common but usually under-recognized among EDS patients. OSA may contribute substantially to fatigue, daytime sleepiness, and impaired quality of life among EDS population.	N/A	N/A	6

(Hagberg et al., 2004)	Sweden	Cross-sectional	144	18/126	44 (42–46)	N/A	Brighton criteria	GHQ12	Normal population	6/10	Oral problems and masticatory muscle symptoms were significantly higher among EDS patient compared with controls. In the EDS group, those who had daily pain in the masticatory muscles had significantly higher mean values on the VAS scales compared with those who had pain a few days per month	45/144	VAS	N/A
(Hakimi et al., 2020)	France	Cross-sectional	21	1/20	45 ± 13	29 ± 6	Self-reported	SF-36	No control	3/10	The study showed that an outpatient rehabilitation program for EDS-HT patients significantly improved functional capacity and quality of life (particularly in the vitality aspect).	N/A	N/A	N/A
(Hope et al., 2019)	Norway	Cross-sectional	49	3/46	40.6 ± 12.6	N/A	Self-reported	SHC-I	Matched healthy controls	5/10	Adults with EDS-HT reported a higher frequency and severity of subjective health complaints than the matched controls from the general adult population in Norway.	N/A	N/A	N/A
(Inayet et al., 2018)	UK	Cohort	45	6/39	24 (18–32)	N/A	Beighton criteria	SF-36	Matched outpatients and Marfan syndrome patients	6/9	EDS-HT group showed a higher prevalence of abdominal symptoms compared to the control group. EDS-HT group showed a more frequent and severe symptoms meeting Rome IV criteria. EDS-HT group scored lower QoL value than the Marfan and control group.	N/A	N/A	N/A
(Jeffery et al., 2021)	USA	Cross-sectional	71	0/68	N/A***	N/A	Beighton criteria	Survey on three main themes	No control	1/10	EDS-HT can affect vocal performance in singers, their professional opportunities, and quality of life.	N/A	N/A	7.19
(Johannessen et al., 2016)	Norway	Cross-sectional	52	3/49	38.7± 12.7	25.1±4.5)	Medical Record	SF-36	Normal population	6/10	EDS-HT patients had lower HRQoL on the SF-36 Physical Component Scale and more pain intensity than controls. EDS-HT patients frequently reported generalized pain.	N/A	NRS	N/A
(Krahe et al., 2018)	Australia	Cross-sectional	117	7/110	35±12.1	N/A	Brighton criteria and Villefranche criteria	AQoL-6D	No control	4/10	Significant fatigue was reported by 79.5% of the participants, significantly correlated with health-related quality of life and mental health measures. Mean value of the total AQoL score was 0.61/1.	76/117	N/A	5.8±1.8

(Lam et al., 2021)	UK	Case-control	603	23/580	39±13	N/A	Self-reported	SF-8	Matched healthy controls	6/10	Almost all EDS patients met the Rome IV functional gastrointestinal disorder criteria, had significant health impairment, and used a tremendous amount of healthcare payment. EDS patients had significantly lower (abnormal) scores in all physical and mental quality-of-life domains.	N/A	N/A	N/A
(Mastoroudes et al., 2013)	UK	Case-control	60	0/60	39.4 (18–60)	N/A	Brighton criteria	P-QOL	Matched healthy controls	9/10	Prolapse symptoms affected a large number of women with EDS and had a significant impact on their quality of life. Prolapse symptoms had a statistically significant impact on quality of life in seven of nine domains of P-QOL. Women with EDS had more severe pelvic organ prolapse (POP).	N/A	N/A	N/A
(Martinez et al., 2021)	USA	Cross-sectional	98	9/89	40.9± 15.0	26.8± 8.3	2017 International Classification Criteria	SF-36	Normal population (unaffected family members)	6/10	EDS patients had a variety of physical and somatic symptoms, particularly in the areas of fatigue, kinesiophobia, gastrointestinal function, and autonomic function. These significantly reduced health-related quality of life.	N/A	N/A	6.5±1.7
(Molander et al., 2020)	Sweden	Cross-sectional	795	51/744	36.2± 10.56	N/A	2017 International Classification Criteria	SF-36 and EQ-5D	Patients who had other chronic pain conditions	6/10	Spinal pain and WAD patients rated their physical health better than EDS patients, but no differences were observed between EDS and fibromyalgia patients. The EDS group showed significant differences in the SF-36 mental health domain, the EQ-5D index, and the EQ-VAS compared to spinal pain and WAD, albeit with a small effect size.	420/795	NRS and MPI	N/A
(Morlino et al., 2019)	Italy	Cross-sectional	105	9/96	36.9± 12.08	N/A	Brighton criteria and Villefranche criteria	FDQ-9 and SF-36	Matched healthy controls	7/10	There was an apparent excess of scores above the FDQ-9 cut-off (>21) in the patient group compared to controls, indicating a positive finding of one or more functional difficulties in the patient group. FDQ-9 was significantly associated with ASRS-V1.1, BPI, COMPASS-31, and SF-36, but not with MFI-20.	N/A	N/A	4.54
(Murray et al., 2013)	USA	Cross-sectional	466	47/419	N/A*	N/A	Self-reported	237-item survey instrument	No control	4/10	Individuals suffering from EDS-HT may experience a wide range of symptoms and comorbidities. Most EDS-HT respondents reported constant pain and disability, demonstrating the impact this disorder has on quality of life.	N/A	McGill pain questionnaire	N/A

(Nee et al., 2019)	Israel	Cross-sectional	1804	110/ 1691*	40.9 ± 13.2	N/A	Self-reported	CDC HRQOL-4	Patients with Marfan syndrome.	6/10	Participants with EDS had remarkably longer unhealthy mental and physical days than participants with Marfan syndrome. The unhealthy days index was significantly greater in patients with EDS than in individuals with Marfan syndrome.	1325/ 1804	N/A	N/A
(Oelerich et al., 2020)	Ger-many	Cross-sectional	46	4/42	39.5 (19-82)	N/A	Self-reported	OHIP-14	No control group	4/10	Patients with EDS had a lower OHRQoL. Participants who experienced tooth, mouth, and jaw pain frequently or very frequently had lower OHRQoL.	24/46	N/A	N/A
(Palomo-Toucedo et al., 2020)	Spain	Cross-sectional	38	5/33	44.07 ± 5.99	26.06 ± 5.75	Self-reported	SF-12	No control group	5/10	The quality of life among EDS patients was generally diminished, with high levels of pain and foot functionality limitations.	31/38	VAS (NRS)	N/A
(Puledda et al., 2015)	Italy	Cross-sectional	33	4/29	32.11 ± 11.63	N/A	Brighton criteria and Villefranche criteria	MIDAS and HIT-6	Control population of migraine patients	7/10	Patients with EDS-HT had a more intense headache syndrome than controls (higher HIT-6 and MIDAS scores).	N/A	NRS	N/A
(Rombaut et al., 2010)	Belgium	Cross-sectional	32	0/32	38 (25–67)	26 (18–38)	Villefranche criteria	SF-36	Matched healthy controls	7/10	EDS-HT was characterized by a variety of severe musculoskeletal complaints and harms both the physical and psychosocial dimensions of physical activity and HRQoL.	N/A	VAS (NRS)	7
(Rombaut, Malfait, De Paepe, et al., 2011)	Belgium	Cross-sectional	72	0/72	40.1 ± 11.94	N/A	Villefranche criteria	SIP	Women with fibromyalgia (FM) and rheumatoid arthritis (RA)	6/10	EDS-HT was associated with a consistent disease burden, comparable to fibromyalgia but worse than rheumatoid arthritis, as well as broad consequences of chronic pain on daily life (measured using SIP and MPI scores).	N/A	MPI	N/A
(Rombaut, Malfait, De Wandele, et al., 2011)	Belgium	Cross-sectional	79	8/71	40 ± 12.7	N/A	Villefranche criteria	SIP	No control group	4/10	Patients with EDS-HT reported a multitude of complaints, a high prevalence of severe pain, and a clinically significant impact of disease on functional status, all of which contributed to their high rate of treatment utilization. The outcome of surgical and physiotherapy treatment was generally disappointing.	N/A	VAS	N/A
(Rombaut et al., 2015)	Belgium	Cross-sectional	23	0/23	40±10.6	N/A	Villefranche criteria	SF-36	Matched healthy controls	6/10	There were different types of pain in EDS-HT and suggested the existence of a central hyperexcitability as an important mechanism involved in the chronic pain problems in this patient group. EDS-HT patients presented with decreased pressure pain thresholds (PPTs) and generalized widespread areas of hyperalgesia.	N/A	PD-Q	N/A

(Verbraecken et al., 2001)	Nether-lands	Cross-sectional	9	3/6	34± 3	23± 1	Self-reported	SF-36	Matched healthy controls	6/10	The SF-36 scores were significantly lower in patient groups, except for the emotional problems domain. Sleep complaints were common in Marfan syndrome and EDS patients, and they correlated well with various QOL items (measured using ESS).	5/9	N/A	N/A
(Voermans et al., 2010)	Nether-lands	Cross-sectional	273	30/243	41 (16-89)	N/A	Self-reported	SIP	No control	4/10	Among EDS patients, chronic pain was highly prevalent, associated with analgesic use, and is more commonly found in the hypermobility type than in the classic type. Pain severity is associated with hypermobility, dislocations, and previous surgeries, contributing to functional impairment in daily life, independent of fatigue levels and low nocturnal sleep quality.	162/273	VAS	N/A
(Zeitoun et al., 2013)	France	Cross-sectional	134	11/123	35±14.7	24.3± 6.1	Villefranche criteria	GIQLI score	Normal population	6/10	Digestive symptoms were prevalent among EDS patients, mostly nonspecific and not serious, but possibly had a significant impact on quality of life.	108/134	N/A	N/A

Note: *Gender data incomplete; **Data were presented as: mean (95% CI) (Berglund et al., 2015); Fikree et al., 2015; Hagberg et al., 2004), Mean (Range) (Berglund & Nordström, 2001; Inayet et al., 2018; Mastoroudes et al., 2013 Voermans et al., 2010), and Median (Range) (Bovet et al., 2016; Fikree et al., 2017 Oelerich et al., 2020; Rombaut et al.; 2010), mean only (Demes et al., 2020); ***No description of age values or presented as age group.

Abbreviation: Adult Attention-deficit/hyperactivity disorder (ADHD Self-Report Scale (ASRS-v1.1), Assessment of Quality of Life (AQoL-6D), Brief Pain Inventory (BPI), Center for Disease Control and Prevention Health-Related Quality of Life-4 Items (CDC HRQOL-4), Composite Autonomic Symptom Score 31 (COMPASS-31), Ehlers-Danlos syndrome (EDS), Ehlers-Danlos syndrome, hypermobility type (EDS-HT), Epworth Sleepiness Scale (ESS), European Quality of Life Instrument (EQ-5D), Functional Difficulties Questionnaire (FDQ-9), Gastrointestinal Quality of Life Index (GIQLI), General Health Questionnaire (GHQ-12), Headache Impact Test-6 (HIT-6), Health-related Quality of Life (HRQoL), Migraine Disability Assessment (MIDAS), Multidimensional Fatigue Inventory 20 (MFI-20), Quality of Life in Neurological Disorders (Neuro-QoL), Numeric Rating Scale (NRS), Obstructive Sleep Apnea (OSA), Oral Health Impact Profile (OHIP-14), Oral health-related quality of life (OHRQoL), Pain Detect Questionnaire (PDQ), Prolapse quality of life (P-QOL), PROMIS Pain Interference (PROMIS-PI), PROMIS Pain Behavior (PROMIS-PB), Short Form-8 quality of life (SF-8), 12-Item Short Form Health Survey (SF-12), 36-Item Short Form Survey (SF-36), Sickness Impact Profile (SIP), Subjective Health Complaints Inventory (SHC-I), Visual Analog Scale (VAS), Whiplash Associated Disorders (WAD)

3.2 Health-related quality of life assessment tools

The SF-36 was the most commonly used HRQoL assessment instrument, used in 17 studies (Albayrak et al., 2015; Berglund et al., 2015; Bovet et al., 2016; Celletti et al., 2013; De Wandele et al., 2014; Demes et al., 2020; Fikree et al., 2015, 2017; Gaisl et al., 2017; Hakimi et al., 2020; Inayet et al., 2018; Johannessen et al., 2016; Martinez et al., 2021; Molander et al., 2020; Rombaut et al., 2010, 2015; Verbraecken et al., 2001), followed by Sickness Impact Profile (SIP) (four studies) (Berglund & Nordström, 2001; Rombaut et al., 2011a; Rombaut et al., 2011b; Voermans et al., 2010) and Oral Health Impact Profile (OHIP-14) (two studies) (Berglund & Björck, 2012; Oelerich et al., 2020). All of the following assessment instruments were only used in one study: Quality of Life in Neurological Disorders (Neuro-QoL) (Arthur et al., 2016), Brief Pain Inventory (BPI) (Bénistan & Martinez, 2019), General Health Questionnaire (GHQ12) (Hagberg et al., 2004), Subjective Health Complaints Inventory (SHC-I) (Hope et al., 2019), The Assessment of Quality of Life (AQoL)-6D (Krahe et al., 2018), Short Form-8 Quality of Life (SF-8) (Lam et al., 2021), Prolapse quality of life (P-QOL) (Mastoroudes et al., 2013), 12-Item Short Form Health Survey (SF-12) (Palomo-Toucedo et al., 2020), Center for Disease Control and Prevention Health-Related Quality of Life-4 Items (CDC HRQOL-4) (Nee et al., 2019), and Gastrointestinal Quality of Life Index (GIQLI) (Zeitoun et al., 2013). Meanwhile, two studies used an unspecified questionnaire to assess QoL (Jeffery et al., 2021; Murray et al., 2013), and three studies utilized more than one type of QoL assessment method (Molander et al., 2020; Morlino et al., 2019; Puledda et al., 2015).

3.3 Impact on health-related quality of life as illustrated by the SF-36

The pooled mean results and standard deviations of the SF-36 domains are presented in Table 2. EDS patients' SF-36 scores were lower across the domains than those of the general population. According to the findings, physical domains of quality of life among individuals with EDS are more affected than mental domains. The average Physical Component Summary (PCS) score was (35.34/100, MD = -31.74; 95% CI = -46.73 to -16.74; $p<0.0001$), while the average Mental Component Summary (MCS) score was (45.21/100, MD = -20.65; 95% CI = -32.30 to -8.99; $p=0.0005$). This data shows that EDS patients were more significantly affected in terms of physical condition than their mental state. All components of physical state, including physical function (MD = -31.36; 95% CI = -49.22 to-13.50; $p=0.0006$), physical role limitation (MD = -57.12; 95% CI = -65.18 to -49.06; $p<0.00001$], bodily pain (MD = -31.81; 95% CI = -49.95 to -13.66; $p = 0.0006$), and general health (MD = -29.26; 95% CI = -45.70 to -12.82; $p=0.0005$) were substantially lower in EDS patients than general population. Similar trend was also observed in the mental component, such as vitality (MD = -24.64; 95% CI = -36.34 to -12.94; p<0.0001), social functioning (MD = -29.14; 95% CI = -42.69 to -15.58; p<0.0001), role emotional (MD = -27.30; 95% CI = -38.86 to -15.74; p<0.00001), and mental health (MD = -12.36; 95% CI = -18.75 to -5.96; p=0.0002. The illustration of differences of SF-36 values among EDS patient and normal population is shown in Figure 2.

Table 2. Meta-analysis of SF-36 values and associated study variables along with correlation analysis

	PF	RP	BP	GH	PCS	V	SF	RE	MH	MCS
Pooled mean	49.01	21.60	37.55	34.76	35.34	28.98	46.69	47.05	60.45	45.21
Standard deviation	28.72	36.98	33.18	24.69	27.55	23.42	30.11	38.58	21.10	24.40
Heterogeneity (I2%)	100	89	99	99	99	99	98	94	95	98
Overall effect (*z*; *p*)	3.44; 0.0006	13.89; <0.00001	3.44; 0.0006	3.49; 0.0005	4.15; <0.0001	4.13; <0.0001	4.21; <0.0001	4.63; <0.00001	3.79; 0.0002	3.47; 0.0005
Correlation[a]										
Age	-0.430	-0.455	-0.407	-0.345	-0.467	**-0.712***	-0.458	-0.468	-0.076	-0.578
Female proportion	**-0.733***	**-0.745***	-0.419	**-0.636***	**-0.867****	-0.491	-0.442	-0.406	-0.212	-0.467
Sample size	0.103	0.164	0.097	-0.103	0.127	0.103	-0.067	-0.479	-0.285	-0.358
Publication year	-0.080	-0.117	-0.142	-0.288	-0.067	-0.609	-0.206	-0.216	-0.176	-0.408
BMI	**-0.757***	-0.476	-0.686	**-0.755***	-0.500	**-0.789***	-0.609	**-0.783***	-0.382	-0.429

Abbreviation; Physical Functioning (PF), Physical Role Limitations (RP), Bodily Pain (BP), General Health (GH), Physical Component Summary (PCS), Vitality (V), Social Functioning (SF), Emotional Role Limitations (RE), Mental Health (MH), Mental Component Summary (MCS)

Note: [a]Correlation analysis was done using Pearson or Spearman

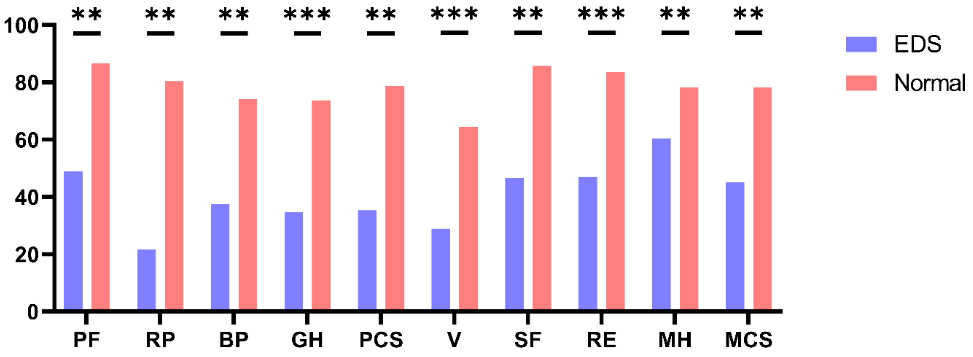

Figure 2. Comparison of Short Form 36 (SF-36) values among EDS patient and normal population.

Abbreviations: Physical Functioning (PF), Physical Role Limitations (RP), Bodily Pain (BP), General Health (GH), Physical Component Summary (PCS), Vitality (V), Social Functioning (SF), Emotional Role Limitations (RE), Mental Health (MH), Mental Component Summary (MCS)

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

3.4 Correlation between observed study variables and health-related quality of life

Pearson's or Spearman's correlation analyses were used to assess the factors associated with HRQoL, including mean participant age, the proportion of female participants, sample size, publication year, and body mass index (BMI) (Table 2). Participant's age was found to have a significant negative correlation with vitality (r = -0.712, p = 0.021). Meanwhile, the proportion of female participants demonstrated significant negative correlations with physical functioning (r = -0.733, p = 0.016), physical role limitations (r = -0.745, p = 0.013), general health (r = -0.636, p = 0.048), and PCS (r = 0.867, p = 0.001). Furthermore, similar correlations were found between BMI with physical functioning (r = -0.757, p = 0.03), general health (r = -0.755, p = 0.03), vitality (r = -0.789, p = 0.02), and emotional role limitations (r = -0.783, p = 0.021).

3.5 Quality assessment

The Newcastle-Ottawa Scale (NOS) was utilized for risk of bias assessment. From the evaluation of case-control and cohort studies, four studies received a high-quality rating (score of 7-9), one study obtained an intermediate grade (score of 4-6), and one study got a low-quality rating (score of 0-3). The NOS instrument was modified for cross-sectional studies to make it more appropriate. Four studies were of high quality (score 7-10), 19 were of intermediate quality (score 5-6), and eight were of low quality (score 0-4). The included studies acquired appraisal scores ranging from 1 to 7 (mean: 5.29±1.32; cross-sectional) and 2 to 8 (mean: 6.5±2.43; case-control and cohort) across three different criteria (selection, comparability, and outcome). Most studies had moderate quality (19/37; 51.35%). Whereas, eight studies have a low risk of bias ratings (21.62%). Meanwhile, same amount of studies have high risk of bias. The comparability domain had the highest risk of bias, with 9 of 37 studies receiving zero stars (attributed to the lack of a control group). Table 3 provides a quality assessment of the included studies.

Table 3. Risk of Bias Assessment

	Selection	Comparability	Outcome	Overall	Risk of Bias
CROSS SECTIONAL					
1	***	*	**	6	Moderate
2	***	**	**	7	Low
4	***	*	*	5	Moderate
5	***	*	*	5	Moderate
6	***	*	*	5	Moderate
8	***	*	*	5	Moderate

9	***	*	**	6	Moderate
12	****	*	*	6	Moderate
15	**	*	*	4	High
18	****	*	*	6	Moderate
19	**	0	*	3	High
20	***	*	*	5	Moderate
22	*	0	0	1	High
23	***	**	*	6	Moderate
25	***	0	*	4	High
26	***	**	*	6	Moderate
28	***	**	*	6	Moderate
29	***	**	*	6	Moderate
30	***	**	**	7	Low
31	***	0	*	4	High
33	***	**	*	6	Moderate
34	***	0	*	4	High
36	***	0	**	5	Moderate
37	***	**	**	7	Low
39	***	**	**	7	Low
40	***	**	*	6	Moderate
41	***	0	*	4	High
42	***	**	*	6	Moderate
46	***	**	*	6	Moderate
49	***	**	*	6	Moderate
50	***	0	*	4	High
CASE-CONTROL/COHORT					
7	**	0	0	2	High
11	***	**	***	8	Low
14	***	**	**	7	Low
17	****	**	*	7	Low
21	***	**	*	6	Low
27	****	**	***	9	Low

3.6 Publication bias assessment

The funnel plot and Egger's linear regression test are used to demonstrate publication bias. From a visual inspection of the Funnel plot, the data distribution is quite symmetrical for all SF-36 variable, indicating the low possibility of publication bias (figure 5). Then, based on the Begg and Mazumdar test and Egger's test, no publication bias was detected (p>0.05) (table 4). Furthermore, from the sensitivity analysis, there was no significant change in the bias analysis, denoting that the finding of the SF-36 component meta-analysis was stable. Nonetheless, due to the high heterogeneity across all studies, it is difficult to conclude the existing publication bias based on the above assessments.

3.7 Meta-regression

Tables 6 and 7 display the findings of the complete model meta-regressions. When combined, year of publication, male/female ratio, and age did not explain any heterogeneity of differences between physical and mental components of SF-36 (p<0.05), except for age and physical function (p=0.04). Univariate meta-regressions on the differences between SF-36 components are also presented in Tables 6 and 7. Similar results were found in the analysis when none of our covariates explained any of the heterogeneity of SF-36 component values (p>0.05), except for age, which influences patients' vitality (10 studies, p=0.03).

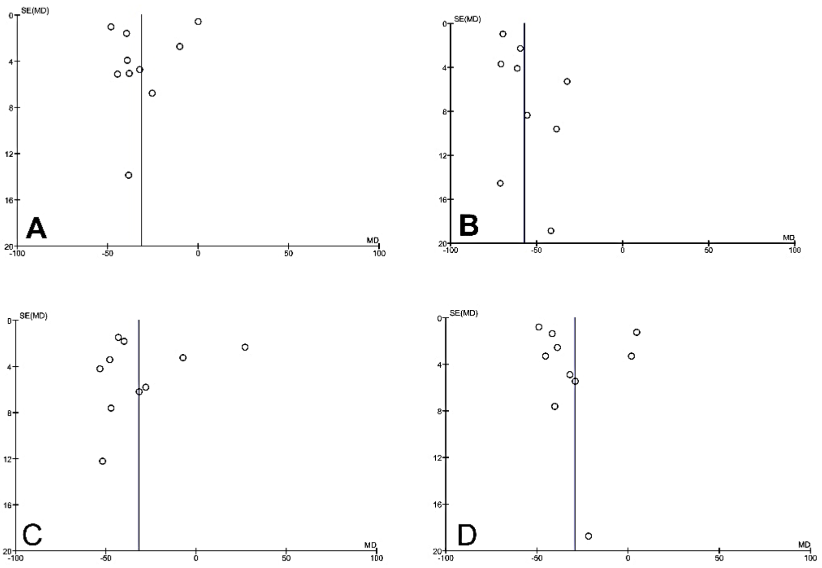

Figure 5a. Funnel plot of SF-36 variables. (A) Physical Functioning, (B) Physical Role Limitations, (C) Bodily Pain, (D).

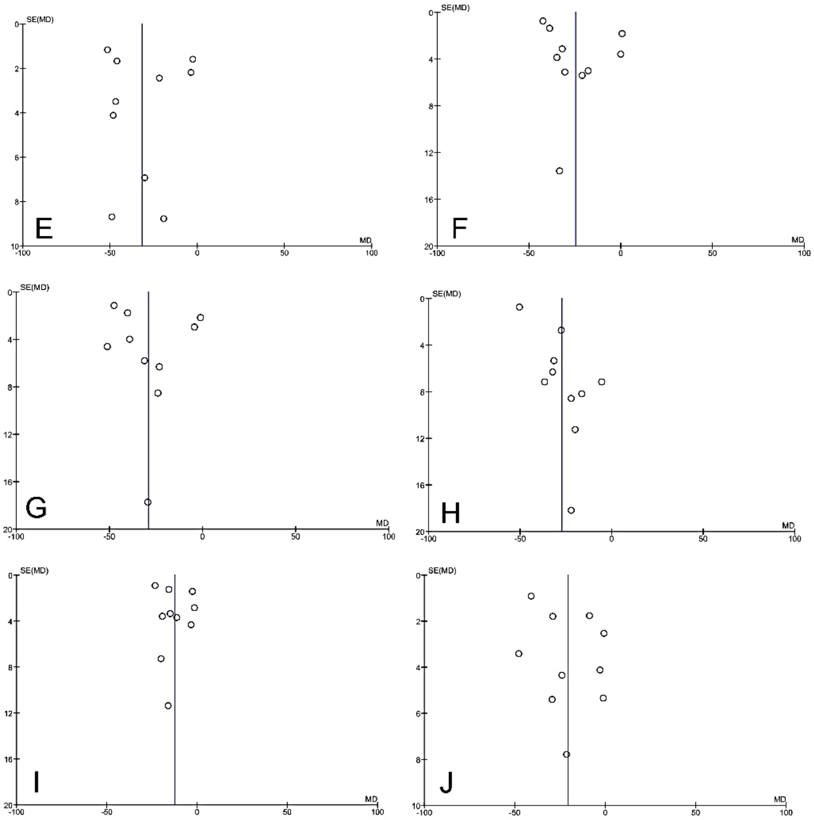

Figure 5b. General Health, (E) Physical Component Summary, (F) Vitality, (G) Social Functioning, (H) Emotional Role Limitations, (I) Mental Health, (J) Mental Component Summary.

Table 4. Publication bias assessment

SF-36 indicator	Begg and Mazumdar test		Egger's test	
	Z-value	P-value	95% CI	P-value
PF	1.073	0.283	-24,675 — 8,329	0.286
RP	0.938	0.348	-33,759 — 14,236	0.368
BP	0.716	0.474	-11.871 — 14.590	0.819
GH	0.358	0.721	-2,972 — 15,279	0.159
PCS	0.464	0.929	-3,646 — 14,270	0.209
V	0.358	0.721	-4,399 — 14,542	0.252
SF	0.537	0.592	-4,224 — 13,204	0.269
RE	0.537	0.592	-0.780 — 6,876	0.104
MH	0.893	0.371	-2.024 — 8.686	0.189
MCS	0.179	0.858	-5,441 — 21,728	0.204

Abbreviation: Physical Functioning (PF), Physical Role Limitations (RP), Bodily Pain (BP), General Health (GH), Physical Component Summary (PCS), Vitality (V), Social Functioning (SF), Emotional Role Limitations (RE), Mental Health (MH), Mental Component Summary (MCS)

Table 5. Meta-regression of the physical component of SF-36

Model	PF			BP			GH			PCS		
	I^2 (%)	R^2	p	I^2 (%)	R^2	p	I^2 (%)	R^2	p	I^2 (%)	R^2	p
No covariate	97.62	-	<0.01	98.88	-	<0.01	99.28	-	<0.01	98.98	-	<0.01
Univariate												
Year	97.33	-	0.11	98.94	-	0.63	99.01	0.04	0.99	98.81	-	0.82
M/F	96.44	0.32	0.96	98.92	-	0.66	99.20	0.09	0.50	98.75	-	0.68
Age	96.86	0.14	0.09	98.35	0.24	0.11	98.71	0.35	0.08	98.06	0.42	0.08
All covariates	95.68	-		98.52	-		98.22	0.20		97.78	0.23	
Year			0.16			0.59			0.88			0.81
M/F			0.28			0.87			0.84			0.65
Age			**0.04**			0.25			0.16			0.13

Abbreviation; Physical Functioning (P), Bodily Pain (BP), General Health (GH), Physical Component Summary (PCS)

Note: We did not conduct the analysis on the Physical Role Limitations due to insufficient study amount (n=9)

Table 6. Meta-regression of the mental component of SF-36

Model	V			SF			RE			MH			MCS		
	I^2	R^2	p	I^2	R^2	p	I^2	R^2	p	I^2	R^2	p	I^2	R^2	p
No covariate	98.35	-	<0.01	98.28	-	<0.01	93.63	-	<0.01	95.78	-	<0.01	98.12	-	<0.01
Univariate															
Year	97.82	0.06	0.67	97.82	-	0.59	79.84	0.55	0.19	92.45	0.25	0.96	97.12	0.16	0.51
M/F	97.95	0.17	0.19	97.58	0.26	0.17	65.94	0.48	0.05	94.65	0.19	0.59	97.96	0.08	0.47
Age	97.09	0.41	**0.03**	97.56	0.19	0.06	94.03	-	0.40	95.20	0.03	0.17	98.10	-	0.41
All covariates	96.35	0.36	0.91	96.3	-	0.82	68.96	0.60	0.49	91.29	-	0.99	97.39	<0.01	0.69
Year			0.90			0.95			0.15			0.67			0.99
M/F			0.12			0.22			0.99			0.17			0.57
Age															

Abbreviation: Vitality (V), Social Functioning (SF), Emotional Role Limitations (RE), Mental Health (MH), Mental Component Summary (MCS)

4. Discussion

The present study investigated the HRQoL among adult EDS patients to gain a better understanding of the patients' experiences. The review's findings indicated that EDS negatively impacted HRQoL and that individuals with the syndrome rated their quality of life much lower than general population. Females were more likely than males to have EDS, especially the hypermobility type (EDS-HT). This is contrary to the autosomal dominant pattern of inheritance of the EDS (which implies an equal number of sufferers representing both genders) (Malfait et al., 2010). However, because women have more complaints (clinical variability) and attend support groups more frequently, there emerges to be a gender bias in the number of impacted women compared to men (Castori et al., 2010). Although the high prevalence of females with EDS-HT is well documented in clinical practice, little is known about the underlying causes of this gender disparity. According to Castori et al., the skewed sex ratio in EDS-HT may have a biological basis (Castori et al., 2010).

This review demonstrated that a variety of HRQoL tools were employed, with 19 assessment tools being utilized. The SF36 was used in nearly half of the included studies (n = 17), indicating some consistency in the methods for assessing HRQoL among EDS patients. The SF-36 is a well-known tool for evaluating patients' quality of life across eight domains. It has also undergone extensive reliability and validity testing (Caruso et al., 2014). The SF-36 is a generalized quality of life questionnaire (Martino et al., 2018), but it does not assess the subtle aspects of HRQoL imposed by EDS, such as impaired memory and cognitive deficits (Baeza-Velasco et al., 2017; Fajardo-Jiménez et al., 2022). This type of questionnaire may be biased for two reasons: (i) it assesses health status without evaluating the importance of each domain, and (ii) it takes a limited approach to the patient's life (primarily related to physical functioning) (Cohen & Biesecker, 2010). Consequently, there is a need to develop a reliable and specific HRQoL evaluation tool for EDS. It is preferable to use a mixture of general and EDS-specific HRQoL instruments because this allows comparison with other health conditions and detection of EDS-specific HRQoL limitations (Both et al., 2007).

The findings of the present study showed how complicated EDS is for those afflicted with it. Notably, the PCS score (35.34/100) was lower than the MCS score (45.21/100), indicating that EDS significantly impacts physical health more than mental health. The most significantly impacted SF-36 domains were vitality (28.98) and physical role restrictions (21.60), which were related to physical health. These findings highlight the importance of awareness for exhaustion, low energy, and difficulty with everyday tasks among EDS patients' perspective, which is attributed to recurring pain or chronic fatigue (Hakim et al., 2017; Ishiguro et al., 2022). EDS patients are frequently given only a psychological explanation for their symptoms, leaving them feeling neglected or ignored (Berglund et al., 2010; Ishiguro et al., 2022).

Compared to the general population, people with EDS reported significantly lower HRQoL across all SF-36 domains (Berglund et al., 2015; Orenius et al., 2022). Physical role limitation was the most affected HRQoL domain compared to the general population. In addition, mental domains, particularly emotional role limitations and social functioning, were also significantly impacted. The reasons for these associations are unknown; however, pain may play a role in increasing the risk of psychiatric disorders among EDS patients (Wasim et al., 2019). These comparisons highlight the large number of symptoms associated with EDS.

The analysis demonstrated a significant negative correlation between the proportion of females and physical functioning ($p<0.05$), physical role ($p<0.05$), general health ($p<0.05$), and physical component summary ($p<0.01$) domains of the SF-36. It is possible to speculate that biological factors may contribute to increased pain or aggravation of other syndrome symptoms. According to a review, females have a greater perception of pain due to their sex hormones (Fillingim et al., 2009; Forghani, 2019). The hormonal influence could also explain the gender bias among adults with EDS-HT. The present review also found significant negative correlations between BMI and physical functioning ($p<0.05$), general health ($p<0.05$), vitality ($p<0.05$), and emotional role ($p<0.05$). According to these findings, the higher the BMI of EDS patients, the less favourable their overall health status. A previous meta-analysis demonstrated that higher BMI values may negatively impact the quality of life (Ul-Haq et al., 2013). Furthermore, paediatric patients with EDS and a higher BMI had worse pain intensity (Pacey et al., 2015). This phenomenon highlights the importance of weight loss in improving quality of life. Similarly, there was a significant negative correlation between age and vitality ($p<0.05$), which is related to the natural physiology of aging. Also, this may indicate that among patients with advanced age, symptoms worsen and they lose their vitality (Gille, 2010). Further longitudinal studies are required to assess the long-term effects of aging on HRQoL (Martino et al., 2018) in these specific patients.

The present review had several limitations. First, the analysis excluded grey literature and studies that were not published in English. Another shortcoming of the review was that a proportion of the included studies (n = 4) failed to report SF-36 PCS and MCS scores. Several data were also unavailable, such as means and standard deviations, which must be converted first using the methods described by Wan et al (2014).

One of the present review's strengths is that it strictly adhered to the PRISMA guidelines. Moreover, inter-rater agreement was excellent and substantially significant. The systematic review included 37 studies from 14 different countries (and a global study), covering a wide range of subjects.

5. Conclusion

The study demonstrated that EDS patients have lower HRQoL levels in all aspects compared to the general population, and this was more pronounced in the physical than mental component of wellbeing. Given the lower HRQoL experienced by those with EDS, the assessment of it is crucial for improving care for this lifelong disorder's sufferers. However, a more systematic and consistent approach is required to investigate the impact of EDS on HRQoL, mainly through the use of a specific instrument based on patient experience. Future research should explore the impact of different patient characteristics, such as the Beighton score, advanced age, and pain intensity, on HRQoL among individuals with EDS. Furthermore, research can be directed toward evaluating the complication of EDS and its impact on the deterioration of physical and mental wellbeing, as well as the development of various non-pharmacological strategies or exercises to help alleviate problems associated with EDS.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any potential conflict of interest.

Authors' contributions

TPU, RS, MEM: Protocol development; TPU: Creation of search strategy; TPU, RS, MEM, MC: Study screening, MC, RM, HS: Data extraction; TPU, RS: Risk of bias assessment; TPU: Data analysis and write up, LM: Data validation; MEM: Visualization; MG, KK, LM: Reviewing and editing completed manuscript. All authors reviewed the results and approved the final version of the manuscript.

References

1. Adjei, A. A., Lopez, C. L., Schaid, D. J., Sloan, J. A., Le-Rademacher, J. G., Loprinzi, … & Ruddy, K. J. (2021). Genetic Variations and Health-Related Quality of Life (HRQOL): A Genome-Wide Study Approach. *Cancers, 13*(4), 716. https://doi.org/10.3390/cancers13040716
2. Albayrak, İ., Yilmaz, H., Akkurt, H. E., Salli, A., & Karaca, G. (2015). Is pain the only symptom in patients with benign joint hypermobility syndrome? *Clinical Rheumatology, 34*(9), 1619–9. https://doi.org/10.1007/s10067-014-2610-6
3. Arthur, K., Caldwell, K., Forehand, S., Davis, K., Arthur, K., Caldwell, K., … & Davis, K. (2016). Pain control methods in use and perceived effectiveness by patients with Ehlers – Danlos syndrome : a descriptive study Ehlers – Danlos syndrome : a descriptive study. *Disability and Rehabilitation, 38*(11), 1063–1074. https://doi.org/10.3109/09638288.2015.1092175
4. Baeza-Velasco, C., Bourdon, C., Polanco-Carrasco, R., de Jouvencel, M., Gely-Nargeot, M.-C., Gompel, A., & Hamonet, C. (2017). Cognitive impairment in women with joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. *Rheumatology International, 37*(6), 937–939. https://doi.org/10.1007/s00296-017-3659-8
5. Bénistan, K., & Martinez, V. (2019). Pain in hypermobile Ehlers-Danlos syndrome: New insights using new criteria. *American Journal of Medical Genetics, Part A, 179*(7), 1226–1234. https://doi.org/10.1002/ajmg.a.61175
6. Berglund, B., Anne-Cathrine, M., & Randers, I. (2010). Dignity not fully upheld when seeking health care: experiences expressed by individuals suffering from Ehlers–Danlos syndrome. *Disability and Rehabilitation, 32*(1), 1–7. https://doi.org/10.3109/09638280903178407
7. Berglund, B., & Björck, E. (2012). Women with Ehlers-Danlos Syndrome Experience Low Oral Health–Related Quality of Life. *Journal of Orofacial Pain, 26*(4), 307–314.
8. Berglund, B., & Nordström, G. (2001). Symptoms and functional health status of individuals with Ehlers-Danlos syndrome (EDS). *Journal of Clinical Rheumatology, 7*(5), 308–314. https://doi.org/10.1097/00124743-200110000-00010
9. Berglund, B., Pettersson, C., Pigg, M., & Kristiansson, P. (2015). Self-reported quality of life , anxiety and depression in individuals with Ehlers-Danlos syndrome (EDS): a questionnaire study. *BMC Musculoskeletal Disorders, 16*, 89. https://doi.org/10.1186/s12891-015-0549-7
10. Both, H., Essink-Bot, M.-L., Busschbach, J., & Nijsten, T. (2007). Critical Review of Generic and Dermatology-Specific Health-Related Quality of Life Instruments. *Journal of Investigative Dermatology, 127*(12), 2726–2739. https://doi.org/10.1038/sj.jid.5701142
11. Bovet, C., Carlson, M., & Taylor, M. (2016). Quality of Life , Unmet Needs , and Iatrogenic Injuries in Rehabilitation of Patients With Ehlers – Danlos Syndrome Hypermobility Type / Joint Hypermobility Syndrome. *American Journal of Medical Genetics, Part A, 170*(8), 2044–2051. https://doi.org/10.1002/ajmg.a.37774
12. Caruso, V., Giammanco, & Gitto, L. (2014). Quality of life and uncertainty in illness for chronic patients. *Mediterranean Journal of Clinical Psychology, 2*(2), 1–12. https://doi.org/10.6092/2282-1619/2014.2.990

13. Castori, M. (2012). Ehlers-Danlos Syndrome, Hypermobility Type: An Underdiagnosed Hereditary Connective Tissue Disorder with Mucocutaneous, Articular, and Systemic Manifestations. *ISRN Dermatology*, *2012*, 1-22. https://doi.org/10.5402/2012/751768
14. Castori, M., Camerota, F., Celletti, C., Grammatico, P., & Padua, L. (2010). Ehlers–Danlos syndrome hypermobility type and the excess of affected females: Possible mechanisms and perspectives. *American Journal of Medical Genetics, Part A, 152*(9), 2406–2408. https://doi.org/10.1002/ajmg.a.33585
15. Celletti, C., Castori, M., La Torre, G., & Camerota, F. (2013). Evaluation of kinesiophobia and its correlations with pain and fatigue in joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type. *BioMed research international*, *2013*, 580460. https://doi.org/10.1155/2013/580460
16. Cohen, J. S., & Biesecker, B. B. (2010). Quality of life in rare genetic conditions: a systematic review of the literature. *American Journal of Medical Genetics, Part A, 152*(5), 1136–1156. https://doi.org/10.1002/ajmg.a.33380
17. De Wandele, I., Calders, P., Peersman, W., Rimbaut, S., De Backer, T., Malfait, F., … & Rombaut, L. (2014). Autonomic symptom burden in the hypermobility type of Ehlers-Danlos syndrome: A comparative study with two other EDS types, fibromyalgia, and healthy controls. *Seminars in Arthritis and Rheumatism, 44*(3), 353–361. https://doi.org/10.1016/j.semarthrit.2014.05.013
18. Demes, J. S., McNair, B., & Taylor, M. R. G. (2020). Use of complementary therapies for chronic pain management in patients with reported Ehlers-Danlos syndrome or hypermobility spectrum disorders. *American Journal of Medical Genetics, Part A, 182*(11), 2611–2623. https://doi.org/10.1002/ajmg.a.61837
19. Demmler, J. C., Atkinson, M. D., Reinhold, E. J., Choy, E., Lyons, R. A., & Brophy, S. T. (2019). Diagnosed prevalence of Ehlers-Danlos syndrome and hypermobility spectrum disorder in Wales, UK: a national electronic cohort study and case–control comparison. *BMJ Open, 9*(11), e031365. https://doi.org/10.1136/bmjopen-2019-031365
20. Fajardo-Jiménez, M. J., Tejada-Moreno, J. A., Mejía-García, A., Villegas-Lanau, A., Zapata-Builes, W., Restrepo, J. E., … & Hernandez, J. C. (2022). Ehlers-Danlos: A Literature Review and Case Report in a Colombian Woman with Multiple Comorbidities. *Genes, 13*(11), 2118. https://doi.org/10.3390/genes13112118
21. Fikree, A., Aktar, R., Grahame, R., Hakim, A. J., Morris, J. K., Knowles, C. H., & Aziz, Q. (2015). Functional gastrointestinal disorders are associated with the joint hypermobility syndrome in secondary care: A case-control study. *Neurogastroenterology and Motility, 27*(4), 569–579. https://doi.org/10.1111/nmo.12535
22. Fikree, A., Aktar, R., Morris, J. K., Grahame, R., Knowles, C. H., & Aziz, Q. (2017). The association between Ehlers-Danlos syndrome—hypermobility type and gastrointestinal symptoms in university students: a cross-sectional study. *Neurogastroenterology and Motility, 29*(3), e12942. https://doi.org/10.1111/nmo.12942
23. Fillingim, R. B., King, C. D., Ribeiro-Dasilva, M. C., Rahim-Williams, B., & Riley III, J. L. (2009). Sex, gender, and pain: a review of recent clinical and experimental findings. *The Journal of Pain, 10*(5), 447–485. https://doi.org/10.1016/j.jpain.2008.12.001
24. Forghani, I. (2019). Updates in Clinical and Genetics Aspects of Hypermobile Ehlers Danlos Syndrome. *Balkan Medical Journal, 36*(1), 12–16. https://doi.org/10.4274/balkanmedj.2018.1113

25. Gaisl, T., Giunta, C., Bratton, D. J., Sutherland, K., Schlatzer, C., Sievi, N., … & Kohler, M. (2017). Obstructive sleep apnoea and quality of life in Ehlers-Danlos syndrome: A parallel cohort study. *Thorax, 72*(8), 729–735. https://doi.org/10.1136/thoraxjnl-2016-209560
26. Gana, K., Cuvelier, M., & Koleck, M. (2021). Quality of life, distrust in health care system and adherence to medical recommendations in patients with fibromyalgia: a latent profile analysis. *Mediterranean Journal of Clinical Psychology, 9*(2), 1–16. https://doi.org/10.13129/2282-1619/mjcp-2953
27. Gille, D. (2010). Overview of the physiological changes and optimal diet in the golden age generation over 50. *European Review of Aging and Physical Activity, 7*(1), 27–36. https://doi.org/10.1007/s11556-010-0058-5
28. Hagberg, C., Korpe, L., Andersson-Norinder, J., & Berglund, B. (2004). Ehlers-danlos syndrome (EDS) focusing on oral symptoms: A questionnaire study. *Orthodontics and Craniofacial Research, 7*(3), 178–185. https://doi.org/10.1111/j.1601-6343.2004.00288.x
29. Hakim, A., De Wandele, I., O'Callaghan, C., Pocinki, A., & Rowe, P. (2017). Chronic fatigue in Ehlers–Danlos syndrome—Hypermobile type. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 175*(1), 175–180. https://doi.org/10.1002/ajmg.c.31542
30. Hakimi, A., Bergoin, C., & Mucci, P. (2020). Immediate and 6-week after effects of a rehabilitation program for Ehlers–Danlos syndrome hypermobile type patients: A retrospective study. *American Journal of Medical Genetics, Part A, 182*(10), 2263–2271. https://doi.org/10.1002/ajmg.a.61772
31. Higgins, J. P. T., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ, 327*(7414), 557–560. https://doi.org/10.1136/bmj.327.7414.557
32. Hope, L., Juul-Kristensen, B., Løvaas, H., Løvvik, C., & Maeland, S. (2019). Subjective health complaints and illness perception amongst adults with Joint Hypermobility Syndrome/Ehlers–Danlos Syndrome-HypermobilityType–a cross-sectional study. *Disability and Rehabilitation, 41*(3), 333–340. https://doi.org/10.1080/09638288.2017.1390695
33. Inayet, N., Hayat, J. O., Kaul, A., Tome, M., Child, A., & Poullis, A. (2018). Gastrointestinal symptoms in marfan syndrome and hypermobile ehlers-danlos syndrome. *Gastroenterology Research and Practice, 2018*, 4854701. https://doi.org/10.1155/2018/4854701
34. Ishiguro, H., Yagasaki, H., & Horiuchi, Y. (2022). Ehlers-Danlos Syndrome in the Field of Psychiatry: A Review. *Frontiers in Psychiatry, 12*, 803898. https://doi.org/10.3389/fpsyt.2021.803898
35. Jeffery, T., Postavaru, G. I., Matei, R., & Meizel, K. 'I Have Had to Stop Singing Because I Can't Take the Pain': Experiences of Voice, Ability, and Loss in Singers With Hypermobility Spectrum Disorders. *Journal of voice: official journal of the Voice Foundation*, S0892-1997. https://doi.org/10.1016/j.jvoice.2021.11.017
36. Johannessen, E. C., Reiten, H. S., Løvaas, H., Maeland, S., & Juul-Kristensen, B. (2016). Shoulder function, pain and health related quality of life in adults with joint hypermobility syndrome/Ehlers-Danlos syndrome-hypermobility type. *Disability and Rehabilitation, 38*(14), 1382–1390. https://doi.org/10.3109/09638288.2015.1102336
37. Krahe, A. M., Adams, R. D., & Nicholson, L. L. (2018). Features that exacerbate fatigue severity in joint hypermobility syndrome/Ehlers–Danlos syndrome–hypermobility type. *Disability and Rehabilitation, 40*(17), 1989–1996. https://doi.org/10.1080/09638288.2017.1323022

38. Lam, C. Y., Palsson, O. S., Whitehead, W. E., Sperber, A. D., Tornblom, H., Simren, M., & Aziz, I. (2021). Rome IV Functional Gastrointestinal Disorders and Health Impairment in Subjects With Hypermobility Spectrum Disorders or Hypermobile Ehlers-Danlos Syndrome. *Clinical Gastroenterology and Hepatology, 19*(2), 277-287.e3. https://doi.org/10.1016/j.cgh.2020.02.034
39. Liana, P., Liberty, I. A., Murti, K., Hafy, Z., Salim, E. M., Zulkarnain, M., & Umar, T. P. (2022). A systematic review on neutrophil extracellular traps and its prognostication role in COVID-19 patients. *Immunologic Research, 70*(4), 449–460. https://doi.org/10.1007/s12026-022-09293-w
40. Malfait, F., Wenstrup, R. J., & De Paepe, A. (2010). Clinical and genetic aspects of Ehlers-Danlos syndrome, classic type. *Genetics in Medicine, 12*(10), 597–605. https://doi.org/10.1097/GIM.0b013e3181eed412
41. Martinez, K. L., Mauss, C., Andrews, J., Saboda, K., Huynh, J. M., Sanoja, A. J., Jesudas, R., Byers, P. H., & Laukaitis, C. M. (2021). Subtle differences in autonomic symptoms in people diagnosed with hypermobile Ehlers–Danlos syndrome and hypermobility spectrum disorders. *American Journal of Medical Genetics, Part A, 185*(7), 2012–2025. https://doi.org/10.1002/ajmg.a.62197
42. Martino, G., Catalano, A., Bellone, F., Langher, V., Lasco, C., Penna, A., … & Morabito, N. (2018). Quality of life in postmenopausal women: which role for vitamin D? *Mediterranean Journal of Clinical Psychology, 6*(2), 1–14. https://doi.org/10.6092/2282-1619/2018.6.1875
43. Mastoroudes, H., Giarenis, I., Cardozo, L., Srikrishna, S., Vella, M., Robinson, D., … & Grahame, R. (2013). Prolapse and sexual function in women with benign joint hypermobility syndrome. *BJOG: An International Journal of Obstetrics and Gynaecology, 120*(2), 187–192. https://doi.org/10.1111/1471-0528.12082
44. McHugh, M. L. (2012). Interrater reliability: the kappa statistic. *Biochemia Medica, 22*(3), 276–282. https://doi.org/10.11613/BM.2012.031
45. Molander, P., Novo, M., Hållstam, A., Löfgren, M., Stålnacke, B. M., & Gerdle, B. (2020). Ehlers–danlos syndrome and hypermobility syndrome compared with other common chronic pain diagnoses—a study from the Swedish quality registry for pain rehabilitation. *Journal of Clinical Medicine, 9*(7), 2143. https://doi.org/10.3390/jcm9072143
46. Morlino, S., Dordoni, C., Sperduti, I., Clark, C. J., Piedimonte, C., Fontana, A., … & Castori, M. (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. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics, 180*(1), 25–34. https://doi.org/10.1002/ajmg.b.32698
47. Murray, B., Yashar, B. M., Uhlmann, W. R., Clauw, D. J., & Petty, E. M. (2013). Ehlers-Danlos syndrome, hypermobility type: A characterization of the patients' lived experience. *American Journal of Medical Genetics, Part A, 161*(12), 2981–2988. https://doi.org/10.1002/ajmg.a.36293
48. Nee, J., Kilaru, S., Kelley, J., Oza, S. S., Hirsch, W., Ballou, S., … & Wolf, J. (2019). Prevalence of Functional GI Diseases and Pelvic Floor Symptoms in Marfan Syndrome and Ehlers-Danlos Syndrome: A National Cohort Study. *Journal of Clinical Gastroenterology, 53*(9), 653–658. https://doi.org/10.1097/MCG.0000000000001173

49. Oelerich, O., Kleinheinz, J., Reissmann, D. R., Köppe, J., & Hanisch, M. (2020). Correlation between oral health-related quality of life and objectively measured oral health in people with ehlers–danlos syndromes. *International Journal of Environmental Research and Public Health, 17*(21), 1–11. https://doi.org/10.3390/ijerph17218243
50. Orenius, T., Kautiainen, H., Louhi, M., Montin, L., Bulbena, A., & Lindgren, K.-A. (2022). Health-Related Quality of Life and Psychological Distress in Patients With Hypermobility Type Ehlers-Danlos Syndrome. *SAGE Open, 12*(2), 21582440221091236. https://doi.org/10.1177/21582440221091237
51. Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan—a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. https://doi.org/10.1186/s13643-016-0384-4
52. Pacey, V., Adams, R. D., Tofts, L., Munns, C. F., & Nicholson, L. L. (2015). Joint hypermobility syndrome subclassification in paediatrics: a factor analytic approach. *Archives of Disease in Childhood, 100*(1), 8–13. https://doi.org/10.1136/archdischild-2013-305304
53. Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., … & Brennan, S. E. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ, 372*, n71. https://doi.org/10.1136/bmj.n71
54. Palomo-Toucedo, I. C., Vázquez-Bautista, C., Munuera-Martínez, P. V, Domínguez-Maldonado, G., Castillo-López, J. M., & Reina-Bueno, M. (2020). Podiatry alterations in Ehlers-Danlos syndrome. *Medicina Clínica, 154*(3), 94–97. https://doi.org/10.1016/j.medcli.2019.05.006
55. Pequeno, N. P. F., Cabral, N. L. de A., Marchioni, D. M., Lima, S. C. V. C., & Lyra, C. de O. (2020). Quality of life assessment instruments for adults: a systematic review of population-based studies. *Health and Quality of Life Outcomes, 18*(1), 208. https://doi.org/10.1186/s12955-020-01347-7
56. Puledda, F., Viganò, A., Celletti, C., Petolicchio, B., Toscano, M., Vicenzini, E., … & Di Piero, V. (2015). A study of migraine characteristics in joint hypermobility syndrome a.k.a. Ehlers–Danlos syndrome, hypermobility type. *Neurological Sciences, 36*(8), 1417–1424. https://doi.org/10.1007/s10072-015-2173-6
57. Rocchetti, M., Bassotti, A., Corradi, J., Damiani, S., Pasta, G., Annunziata, S., … & Brondino, N. (2021). Is the Pain Just Physical? The Role of Psychological Distress, Quality of Life, and Autistic Traits in Ehlers-Danlos Syndrome, an Internet-Based Survey in Italy. *Healthcare, 9*(11), 1472. https://doi.org/10.3390/healthcare9111472
58. Rombaut, L., Malfait, F., Cools, A., De Paepe, A., & Calders, P. (2010). Musculoskeletal complaints, physical activity and health-related quality of life among patients with the EhlersDanlos syndrome hypermobility type. *Disability and Rehabilitation, 32*(16), 1339–1345. https://doi.org/10.3109/09638280903514739
59. Rombaut, L., Malfait, F., De Paepe, A., Rimbaut, S., Verbruggen, G., De Wandele, I., & Calders, P. (2011a). Impairment and impact of pain in female patients with Ehlers-Danlos syndrome: A comparative study with fibromyalgia and rheumatoid arthritis. *Arthritis and Rheumatism, 63*(7), 1979–1987. https://doi.org/10.1002/art.30337

60. Rombaut, L., Malfait, F., De Wandele, I., Cools, A., Thijs, Y., De Paepe, A., & Calders, P. (2011b). Medication, surgery, and physiotherapy among patients with the hypermobility type of ehlers-danlos syndrome. *Archives of Physical Medicine and Rehabilitation, 92*(7), 1106–1112. https://doi.org/10.1016/j.apmr.2011.01.016
61. Rombaut, L., Scheper, M., De Wandele, I., De Vries, J., Meeus, M., Malfait, F., … & Calders, P. (2015). Chronic pain in patients with the hypermobility type of Ehlers–Danlos syndrome: evidence for generalized hyperalgesia. *Clinical Rheumatology, 34*(6), 1121–1129. https://doi.org/10.1007/s10067-014-2499-0
62. Smits-Engelsman, B., Klerks, M., & Kirby, A. (2011). Beighton score: a valid measure for generalized hypermobility in children. *The Journal of Pediatrics, 158*(1), 119–123. https://doi.org/10.1016/j.jpeds.2010.07.021
63. Sobey, G. (2014). Ehlers–Danlos syndrome – a commonly misunderstood group of conditions. *Clinical Medicine, 14*(4), 432–436. https://doi.org/10.7861/clinmedicine.14-4-432
64. Tadrous, R., O'Rourke, D., Mockler, D., & Broderick, J. (2021). Health-related quality of life in narcolepsy: A systematic review and meta-analysis. *Journal of Sleep Research, 30*(6), e13383. https://doi.org/10.1111/jsr.13383
65. Tinkle, B., Castori, M., Berglund, B., Cohen, H., Grahame, R., Kazkaz, H., & Levy, H. (2017). Hypermobile Ehlers–Danlos syndrome (a.k.a. Ehlers–Danlos syndrome Type III and Ehlers–Danlos syndrome hypermobility type): Clinical description and natural history. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 175*(1), 48–69. https://doi.org/https://doi.org/10.1002/ajmg.c.31538
66. Ul-Haq, Z., Mackay, D. F., Fenwick, E., & Pell, J. P. (2013). Meta-analysis of the association between body mass index and health-related quality of life among adults, assessed by the SF-36. *Obesity, 21*(3), E322–E327. https://doi.org/10.1002/oby.20107
67. Umar, T. P., Samudra, M. G., Nashor, K. M. N., Agustini, D., & Syakurah, R. A. (2022). Health professional student's volunteering activities during the COVID-19 pandemic: A systematic literature review. *Frontiers in Medicine, 9*, 797153. https://doi.org/10.3389/fmed.2022.797153
68. Velasco, C. B., Bourdon, C., Montalescot, L., Cazotte, C. De, & Pailhez, G. (2018). Low- and high-anxious hypermobile Ehlers–Danlos syndrome patients: comparison of psychosocial and health variables. *Rheumatology International, 38*(5), 871–878. https://doi.org/10.1007/s00296-018-4003-7
69. Verbraecken, J., Declerck, A., Van De Heyning, P., De Backer, W., & Wouters, E. F. M. (2001). Evaluation for sleep apnea in patients with Ehlers - Danlos syndrome and Marfan: A questionnaire study. *Clinical Genetics, 60*(5), 360–365. https://doi.org/10.1034/j.1399-0004.2001.600507.x
70. Vita, R., Caputo, A., Quattropani, M., Watt, T., Feldt-Rasmussen, U., Puleio, P., … & Martino, G. (2020). Quality of life in patients with hyperthyroidism: Where do we stand? *Mediterranean Journal of Clinical Psychology, 8*(2), 1–28. https://doi.org/10.6092/2282-1619/mjcp-2521
71. Voermans, N. C., Knoop, H., Bleijenberg, G., & van Engelen, B. G. (2010). Pain in Ehlers-Danlos syndrome is common, severe, and associated with functional impairment. *Journal of Pain and Symptom Management, 40*(3), 370–378. https://doi.org/10.1016/j.jpainsymman.2009.12.026

72. Wan, X., Wang, W., Liu, J., & Tong, T. (2014). Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology, 14*, 135. https://doi.org/10.1186/1471-2288-14-135

73. Wasim, S., Suddaby, J. S., Parikh, M., Leylachian, S., Ho, B., Guerin, A., & So, J. (2019). Pain and gastrointestinal dysfunction are significant associations with psychiatric disorders in patients with Ehlers–Danlos syndrome and hypermobility spectrum disorders: a retrospective study. *Rheumatology International, 39*(7), 1241–1248. https://doi.org/10.1007/s00296-019-04293-w

74. Yin, S., Njai, R., Barker, L., Siegel, P. Z., & Liao, Y. (2016). Summarizing health-related quality of life (HRQOL): development and testing of a one-factor model. *Population Health Metrics, 14*, 22. https://doi.org/10.1186/s12963-016-0091-3

75. Zeitoun, J. D., Lefèvre, J. H., De Parades, V., Séjourné, C., Sobhani, I., Coffin, B., & Hamonet, C. (2013). Functional digestive symptoms and quality of life in patients with Ehlers-Danlos syndromes: Results of a national cohort study on 134 patients. *PLoS ONE, 8*(11), 1–8. https://doi.org/10.1371/journal.pone.0080321

DOI: 10.13129/2282-1619/mjcp-3665