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The Impact of living with Ehlers-Danlos Syndrome on health-related quality of life: A systematic review following the 2017 international EDS classification

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ABSTRACT

Objective: The Ehlers-Danlos Syndromes (EDS) are a group of multi-systemic, chronic conditions with complex symptomology. This systematic review aimed to synthesise what is known about the impact of EDS on Health-Related Quality of Life (HRQoL), and associated moderating factors, following a change in diagnostic criteria.
Methods: Fifteen databases, grey literature and reference lists were systematically searched. A systematic review was performed following the Preferred Reporting Items for Systematic Reviews and guidelines for narrative synthesis. Findings were grouped according to outcomes, moderating factors, and measurement instrument. A further synthesis aligned outcomes with domains of HRQoL. Risk of bias was addressed using the Effective Public Health Practice Project assessment tool.
Results: Eight quantitative studies met eligibility criteria. Findings indicate substantial impact due to symptoms and functional status. However, how HRQoL is measured potentially introduces bias such that other factors are overlooked.
Conclusion: This review suggests key aspects of how HRQoL is experienced remain underexplored and under-reported. Issues of methodological rigour raise further concerns around the usefulness of study findings. Further research is required to clarify how aspects of HRQoL are prioritised and experienced and how they can best be measured, to improve management of this debilitating condition.
PROSPERO registration number CRD42022318979

1. Introduction

Ehlers-Danlos Syndrome (EDS) is a hereditary connective tissue disorder [1] affecting 1 in 5000 of the global population [2,3]. Thirteen subtypes are recognised within the 2017 International Classification [4]. Of these, Hypermobile EDS (hEDS) accounts for 80 % of cases [5] and is distinguished from other subtypes in that its genetic cause has not been identified [4] such that a molecular diagnosis is not available.

Notwithstanding differences in presentation, multisystemic symptomology overlaps across subtypes [6], including joint hypermobility and muscular skeletal complications [7], including joint dislocation, gastrointestinal dysfunction [8,9] and urogynaecological complaints [10,11]. Chronic pain [12,13], sleep deprivation, and fatigue [14,15] are widespread, often accompanied by depression and anxiety [16,17]. Numerous comorbidities [18] exacerbate symptoms [19–21], including neurodevelopmental conditions [22–24]. Consequently, symptomology impacts many activities of daily living. Pain [25], fatigue, fear of injury [26,27], eating difficulties [8,26,28], and unpredictability of symptoms [26] have been shown to hamper engagement in occupational [29], social [30] and other activities [26,31]. EDS is associated with low self-worth [32] compounded by a long diagnostic journey [33]. Consequently, EDS is evidenced to have considerable impact on Health-Related Quality of Life (HRQoL) [34–36].

HRQoL is an important measure in assessing individual and population health and wellbeing and the effectiveness of medical interventions [37], albeit components are disputed [38]. Wilson and

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Cleary [39] proposed a model containing five elements: biological and physiological influences, symptoms, functional status, general health perceptions and overall Quality of Life (QoL), a measurement of subjective wellbeing. Ferrans et al. [40] added causal connections for two further variables, individual and environmental characteristics, where individual characteristics include demographic, psychological and biological factors, and environmental, external aspects, including environment, social and cultural factors. Causal connections in both models are well evidenced [41,42]. However, within the context that HRQoL is influenced by personal preferences [43] and is condition-specific [44,45], how HRQoL is experienced in EDS populations is likely complex and nuanced. Therefore, despite the importance of HRQoL as an outcome measure, the variation in definition and condition-specific experiences are potentially problematic. Consequently, research needs to assess not just the impact of EDS on HRQoL but how this is assessed within the evidence base.

To date, no systematic review has considered both the quantitative impact and perceived experience of HRQoL through a mixed-methods approach for people living with EDS. This is problematic for a condition where treatment options are limited, often ineffective [32,46,47] leaving health needs unmet [34]. Better understanding of the factors that impact HRQoL is needed to improve decisions around condition management. Moreover, understanding around EDS is affected by reclassification, undertaken three times in three decades [48,49]. The most recent, in 2017 [4], excluded those with Joint Hypermobility Syndrome (JHS) from the hEDS subtype[1]. Estimated to affect between 1 % and 2 % of White individuals [1,50], the JHS population is considerably larger than those living with hEDS and was subsequently recategorized within a new group of non-syndromic Hypermobility Spectrum Disorders (HSD) [1]. It was hoped that the new classification would provide a framework for future research. Consequently, this review is required and timely, such that outcomes are specific to this latest classification. Hence this Systematic Review sought to i. establish what is known about how HRQoL is impacted in populations diagnosed post 2017 through a synthesis of quantitative, qualitative, and mixed methods studies, ii. explore findings pertinent to moderating factors, and iii. clarify mechanisms for how HRQoL is measured or captured for people with EDS. The review addresses the question, how is HRQoL experienced and impacted in adults living with Ehlers-Danlos Syndrome?

2. Methods

This review was registered on the International Prospective Register of Systematic Reviews, PROSPERO (CRD42022318979) and completed in accordance with Preferred Reporting Items for Systematic Reviews [51].

2.1. Search strategy and information sources

Free-text search terms around HRQoL concepts were developed and refined in consultation with EDS stakeholders. A Boolean search was devised in MEDLINE and adapted to other databases. A systematic literature search was conducted between December 2022 and January 2023 across online databases: MEDLINE, CINAHL with full text, PsychInfo, PsychArticles, ClinicalTrials.gov, Cochrane Library, ERIC, JStor, NHS Evidence, NICE Evidence, PEDro, PubMED, Science Direct, SportsDiscus and Web of Science. A search of Dissertations, theses and grey literature was conducted (see supplementary materials strategy). Email alerts were created, and studies incorporated until August 31st, 2023. Records were transferred to a reference manager (EndNote 20) and duplicates removed.

2.2. Eligibility criteria

Applying the PICO (Population, Phenomenon of Interest, Context) [52], qualitative, quantitative, and mixed methods studies were included if they reported in English, and included outcomes or experiences of:

(1) human, adults (>18) living with Ehlers-Danlos Syndrome,
(2) where Ehlers-Danlos Syndrome is defined by the categories of the 2017 International Classification,
(3) where at least 60 % of the population are adults who live with EDS or the study allows for disaggregated data,
(4) and where HRQoL or QoL is specified in the aims of the study, explicitly measured in the study, reported in the findings of the study or the discussion had some aspect specifically related to HRQoL/QoL.

2.3. Study selection

Following deduplication and removal of first-stage exclusions (JF), records were transferred to a collaborative database (Rayyan) and a further deduplication completed. Two reviewers (JF and DSW) conducted primary screening of abstracts against eligibility criteria. Secondary screening was conducted independently by two authors (JF and DSW). In cases of ambiguity, clarification was sought from study authors. A third author reviewed conflicts. Final inclusion was based on consensus between JF and EW.

2.4. Data extraction and management

Using Excel, the following data were extracted into a predefined spreadsheet: authors, country of study, publication year, study type, eligibility criteria, design, aims, EDS subtypes, population size, with justification, and demographics, HRQoL/QoL instrument, HRQoL/QoL outcomes and whether primary or secondary, findings significant to review objectives, moderating factors and reported limitations.

2.5. Assessment of methodological quality

Methodological quality was assessed against six domains with a rating of weak, moderate, or strong, using the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool for Quantitative studies [53].

2.6. Assessment of HRQoL/QoL conceptual and methodological rigour

Studies were appraised for conceptual and methodological criteria [54]. Instruments were evaluated for factors such as a global QoL rating or personal preference, reflecting a characterisation of HRQoL as subjective and driven by satisfaction with life [40]. Summary scores were derived from the percentage of eligible criteria each study fulfilled.

2.7. Study synthesis

Meta-analysis was precluded due to heterogeneity. In the absence of qualitative or mixed-method studies, planned meta-integration was replaced with narrative synthesis [55]. Three processes were followed: preliminary synthesis, exploration of relationships and assessment of the robustness of evidence. Synthesis focused on HRQoL reported outcomes, moderating factors, measurement tools and appropriateness. Findings were synthesised according to quality appraisal, EDS subtype, moderating factors, and measurement instrument. Due to the heterogeneity of the latter, a further synthesis was undertaken aligning instrument domains to HRQoL concepts [40], to ascertain outcomes pertinent to HRQoL and demonstrate aspects of HRQoL measured.

3. Results

3.1. Included studies

After removal of duplicates and preliminary screening, 2559 studies were selected. The search initially incorporated publications from 1998 in line with the Villefranche classification of EDS [49]. Records prior to 2017 were removed during review of titles. Following a second screening of abstracts, 508 studies were selected. After full text screening, 500 were excluded, most frequently because HRQoL/QoL were not measured or reported, a lack of clarity regarding EDS classification or the sample was inapplicable. Eight papers were included in the review (see flow diagram Fig. 1).

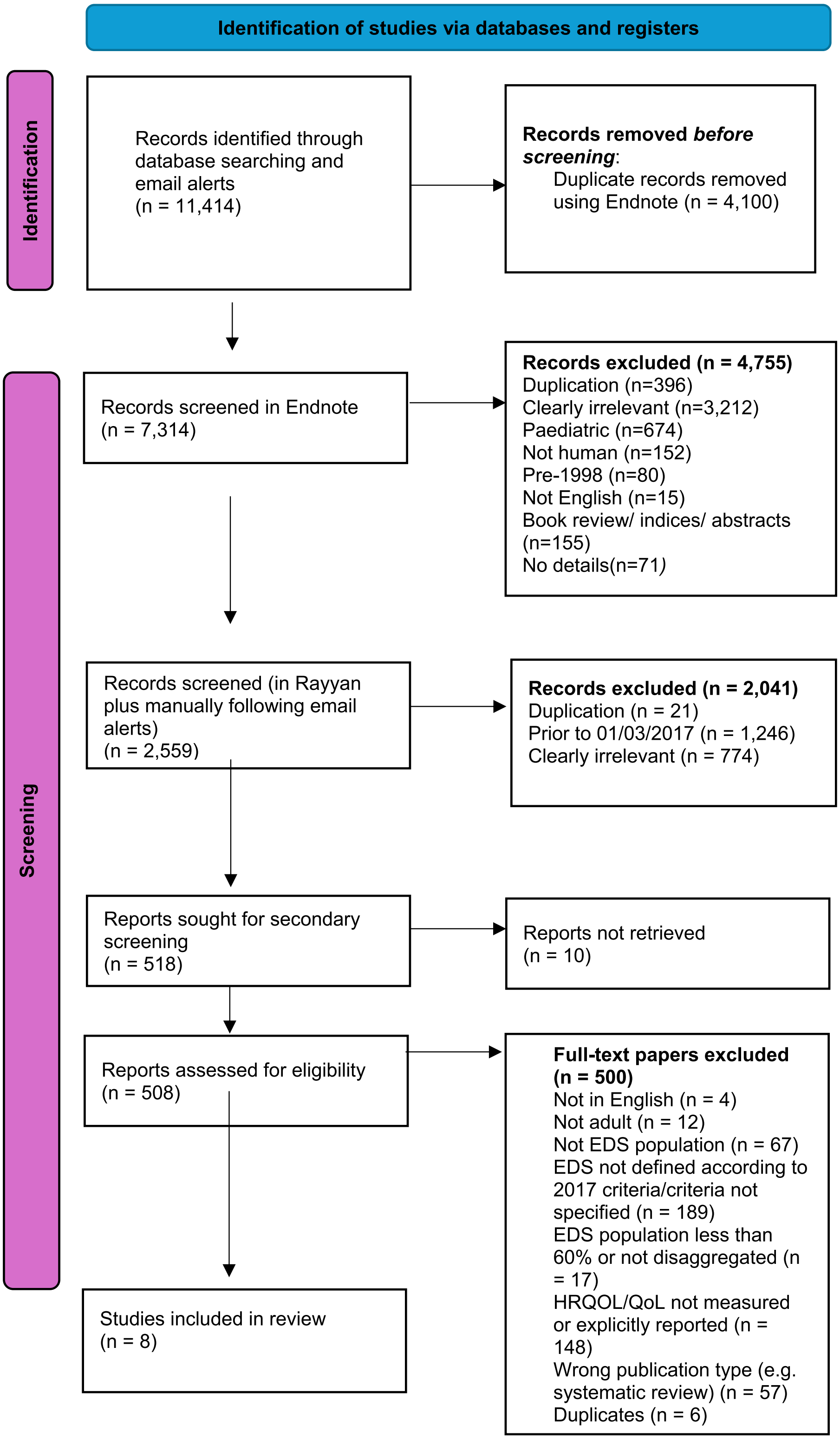

Fig. 1. PRISMA flow diagram of study selection process.

3.2. Study characteristics

3.2.1. Design

The eight quantitative papers incorporated one case control study [56], two longitudinal cohort studies [57,58] and five cross-sectional studies [59–63] (Table 1). One study was undertaken in the United States [61], with the remainder in Europe. Five studies addressed QoL or HRQoL as primary outcomes [58,59,61,62,63]. For the remaining three [56,57,60] exploration of the components or impact of pain was the primary focus. Sample sizes ranged from 19 to 295 participants (M=93.4 SD = 90.8), causing differences in outcome reporting.

3.2.2. EDS population

Studies incorporated 692 people with EDS across ten subtypes (Table 2). Two studies confirmed EDS classification through molecular diagnosis [56,62], one self-report [59] and the remainder clinical review. Three studies [57,59,63] recruited multiple subtypes (Table 1). Participants with hEDS were represented in six studies, two exclusively [58,60] and four [57,59,61,63] in combination with other subtypes. Participants with Classical EDS (cEDS) were included in four studies [56,57,59,63], one solely focused on a cEDS population [56]. Three studies included participants with vEDS, [59,62,63], in one [63] comprising 2 % of the population with non-disaggregated data hence no conclusions specific to vEDS could be drawn. Most prevalent subtypes were hEDS, cEDS and vEDS. Prevalence of other subtypes was below or equal to 1 %.

3.2.3. Population demographics

Age and gender were reported in all studies. Populations were predominantly female, ranging from 61 % to 97 % ($M = 84$ %, $SD = 13.4$). Mean ages ranged from 26 (+/-10) to 45 (+/- 12). Considerable diversity existed in the composition of other demographic information (Table 1) which included BMI in five studies, diagnostic history in five, employment status in four, physical symptoms in three, education in two, family status and previous surgery each in one. Only one study [59] gathered data on comorbidities, although details of type were not presented.

3.2.4. HRQoL/QoL instruments

Six instruments were used to measure HRQoL/QoL outcomes, (Table 3], five generic and one [59] condition-specific (the Oral Health Impact Profile, OHIP-14; [64]. The SF-36 [65] and shorter SF-12 [66] were used in four studies, two to assess QoL and two, HRQoL. Two instruments, the WHOQOL-BREF [67] and LiSAT-11 [68] explicitly measure QoL and Life Satisfaction. The OHIP-14 was designed to measure Oral Health-Related Quality of Life (OHRQoL). The Brief Pain Inventory (BPI) [69] which measures intensity and interference of pain, was also used by Bénistan & Martinez [60] to assess QoL Between them the seven instruments comprised 32 individual domains.

3.3. Methodological quality

Based on the EPHPP, five studies were appraised weak in quality, two moderate and one strong (Table 4). However, the strong study (Colman et al.) [56] was disadvantaged by small sample size, powered for a primary outcome rather than secondary HRQoL measure. Weak study design negatively impacted the two moderate studies, compounded by lack of clarity around confounding factors and reporting of blinding. One weak-quality study (Bénistan et al., 2023) [57] was further hampered by protocol deviation, the other (Rocchetti et al.) [63] assessed at risk of selection bias.

3.4. HRQoL/QoL methodological and conceptual rigour

Using the methodological review developed by Gill and Fernstein [54,70], weaknesses in conceptual rigour were identified in HRQoL/QOL theory and measurement (Table 5). Only three studies [59,61,62] satisfied one or two of the ten criteria. Consequently, the application of HRQoL/QoL concepts across all was rated weak.

3.5. Study reported findings

All studies demonstrated impaired QoL or HRQoL in EDS populations. Colman et al., [56] recorded significant impairment as a secondary outcome (p-values between <.001 and <.032) for all SF-36 domains except Role Limitations due to Emotional Problems (RLEP) for a cEDS cohort when compared to a control. Four studies found impaired HRQoL/QoL against population norms. Balke et al., [59] recorded diminished outcomes for OHRQoL for all included EDS subtypes ($M = 19.6$, $SD = 12.3$) against a mean score of 10.9, exceeded by only 10 % of the wider population [71]. Johansen et al., [62] investigated the impact of vEDS on life satisfaction for a Norwegian cohort, recording significant impairment against Swedish population norms (45 % v 79 %). Martinez et al., [61] showed significantly lower HRQoL ($p < .001$) across all domains. Rocchetti et al., [63] indicated impaired Qol (< 70) for three subtypes across all four Physical Health, Psychological, Social Relationship and Environmental domains of the WHOQOL-BREF, for 80.57 %, 72.66 %, 71,22 % and 82.73 % of the EDS population respectively. Furthermore, Bénistan & Martinez [60] indicated an impact of pain on all measured activities of daily life: General Activity ($M = 7.4$, $SD = 2.1$), Mood ($M = 5.5$, $SD = 3.2$), Walking ability ($M = 7.1$, $SD = 2.5$), Normal work ($M = 7.9$, $SD = 2.1$), Relation with other people ($M = 4.8$, SD = 3.1), Sleep ($M = 6.5$, $SD = 2.7$) and, least impacted, Overall enjoyment of life ($M = 3.6$, $SD = 2.7$). (These scores were estimated from a figure and may display a small margin of error). Two studies were longitudinal, in one, (Hakimi et al.) [58] two assessments taken nine weeks apart and prior to an intervention illustrate consistently low QoL in a hEDS population. Bénistan et al., [57] assessed QoL as a secondary measure in a study of therapeutic effectiveness of compression garments. Measurements over two years demonstrated poor QoL notwithstanding the intervention.

3.6. Findings by HRQoL concepts

To compare outcomes and impact, instrument domains were classified according to six components from the Ferrans et al. (2005) model of HRQoL and presented as follows: Functional Status (FS), Symptoms (S), General Health Perceptions (GHP), Individual Characteristics (IC), Environmental Characteristics (EC), and QoL (Table 6). Biological Function, the seventh component, would typically be measured though medical assessment, beyond the scope of self-report instruments. This reclassification demonstrated that 30 of the 59 domains wholly or partly aligned within the HRQoL component of FS. Perception of Symptoms was associated with 19, GHP with six, IC with six and EC and QoL both with three.

3.6.1. Functional Status (FS)

All studies measured aspects of living with EDS that could be classified in physical functioning (Table 7). Three studies [58,60,61] record most impact on HRQoL in the FS component through the BPI normal work domain and SF-36 RLPH domain. Balke et al. [59] recorded negative impact on activities related to eating and diet. Additionally, a third of participants had frequent difficulty pronouncing words, some, difficulty completing everyday tasks. A small proportion (5.4 %, n = 17) felt unable to do anything. In contrast, 89 % (n = 16) of participants with vEDS recorded scores equivalent to population norms for activities of daily life [62]. Only studies using the SF36 or SF12 reported on the concept of RLEP. Three with hEDS or predominantly hEDS participants [58,60,61] reported negative associations. However, Colman et al. [56] found no impact for a cEDS population. Impact on social functioning and relationships was also measured across all studies. All except two (Bénistan et al., 2023; Johansen et al.) [57,62] recorded a negative impact or association. For one mixed subgroup Rocchetti et al. [63],

Table 1
Study characteristics.

Authors (Yr.) (Country)	Design	Population size/ subgroups/ recorded demographics	EDS verification	QoL measure	Primary/ secondary	Key QoL/HRQoL findings
Bénistan & Martinez (2019) France	Cross-sectional	**Sample size: n = 37** (hEDS) **Demographics recorded.** **Age:** M = 26 (+/−10) [10–53] Gender: F/M 36/37 97 % BMI Physical symptoms Diagnostic history	Clinical	BPI	Secondary	The impact of pain on quality of life was important with a median BPI score of 61 ± 23 and interfered with all aspects of life
Bénistan et al. (2023) France	Cohort study	**Sample size: n = 67** hEDS n = 61, cEDS n = 4, kEDS n = 2 **Demographics recorded.** Age: M = 33.1 (+/- 11.2) [16–60] Gender: F/M 61/6 91 % BMI Employment status Diagnostic history	Clinical	SF−12	Secondary	67.2 % reported mediocre/poor health, 58.2 %; had significant difficulty with everyday activities. The majority felt that their emotional (53.7 %) or physical state (88.1 %) prevented them from doing certain things. 73.1 % recorded pain as very bothersome at work or during activities at home.
Balke et al. (2023) Germany, Austria, Switzerland	Cross-sectional	**Sample size: n = 295** hEDS n = 230, cEDS n = 29, vEDS n = 18, clEDS n = 7, pEDS n = 3, aEDS n = 2, kEDS m = 2, mEDS n = 2, cvEDS n = 1, BCS n = 1 **Demographics recorded.** Age: M = 39.2 (+/−11.2) [18–64] Gender: F/M 270/19 91.5 %/6.4 % Diverse: 6/2 % Diagnostic history Comorbidities	Self-report	OHIP−14 (German version)	Primary	OHRQoL diminished across all subtypes (19.6 ± 12.3), with “Orofacial Pain” having the highest impact (4.26 ± 2.28). No significant differences between subtype could be shown
Colman et al. (2023) Belgium	Case control study	**Sample size: n = 38** cEDS n = 19, Ctrl n = 19 **Demographics recorded.** Age: M = 38.4 (+/−13.1) Gender: F/M 13/6 68 % BMI Employment status Physical symptoms Education	Molecular	SF−36 (Dutch version)	Secondary	Participants with cEDS g scored significantly worse compared to control on all subscales (p-value between <0.001 and 0.032), except for RLEPs (p = 0.26).
Hakimi et al. (2023) France	Cohort study	**Sample size: n = 19 (hEDS)** **Demographics recorded.** Age: M = 45 + /−12) Gender: F/M 18/1 95 % BMI	Clinical	Medical Outcome Study SF−36	Primary	Significant improvement immediately post programme for QoL for physical functioning, RLEP, health change and MCS. Improvement sustained in short-term for physical functioning, vitality, emotional well-being, social functioning, general health, health change and MCS. At 6 months, improvement was limited to physical functioning.
Rocchetti et al. (2021) Italy	Cross-sectional	**Sample size: n = 156** cEDS n = 89, hEDS n = 47, vEDS n = 3, sEDS n = 17 **Demographics recorded.** Age: M = 40 (+/−11.65) Gender: F/M 132/24 78 % Employments status Diagnostic history	Clinical	WHOQOL-BREF	Primary	Mean scores of all domains were indicative of impaired QoL/ severely impaired for 81.4 %/ 17.94 % (Physical Health); 73.71 % /19.23 % (Psychological) 73.71 %/19.23 (Social Relationship), and 83.33 %/ 14.74 % (Environment).
Martinez et al. (2021) USA	Cross sectional	**Sample size: n = 148** hEDS n = 98, HSD n = 27, asymptomatic family members n = 23 **Demographics recorded.** Age: hEDS – M = 41 HSD M = 38 Gender: hEDS F/M 89/9 90.8 % HSD: F/M 22/27 81.5 % AFM: F/M 11/23 48.8 % BMI Physical symptoms Diagnostic history	Clinical evaluation	SF−36	Primary	The mean total scores were significantly lower in all sub- scales for people with hEDS/HSD than those of unaffected participants and population norms
Johansen et al. (2021) Norway	Cross-sectional	**Sample size: n = 52** vEDS n = 18 LDS n = 34 **Demographics recorded.** Age: Median = 38, Quartiles (35.3) [19–68] Gender: F/M 11/18 61 % Employment status Diagnostic history Family status Education	Molecular	LiSat−11	Primary	In line with population norms, vEDS participants were satisfied with family lives (66 %), ADL (89 %), and their relationships with their partners (64 %). Less satisfied than population norms with sexual lives (50 %,) somatic health (33 %,) and vocations (29 %).

Table 2
Ehlers-Danlos Syndrome (EDS) diagnosis status.

EDS subtype	Acronym	Studies *n*	Total *n* (%)
Classical EDS	cEDS	4	141 (20.4)
Classical-like EDS	clEDS	1	7 (1)
Cardiac-valvular EDS	cvEDS	1	1 (0.1)
Vascular EDS	vEDS	3	39 (5.6)
Hypermobile EDS	hEDS	7	492 (71.1)
Anthrochalasia EDS	aEDS	1	2 (0.3)
	dEDS	0	0
Kyphoscoliotic EDS	kEDS	2	4 (0.6)
Brittle Cornea Syndrome	BCS	1	1 (0.1)
	spEDS	0	0
	mcEDS	0	0
Myopathic EDS	mEDS	1	2 (0.3)
Periodontal EDS	pEDS	1	3 (0.4)

Note. Dermatosparaxis EDS, Musculocontractural EDS, and Spondylodysplastic EDS were not included among participants of the eligible studies.

poor outcomes for social participation were recorded through both the WHOQOL-BREF Environment domain, encompassing attitudes towards recreation, and the Social Relationships domain, incorporating outlooks around personal and sexual relationships. This was corroborated in a vEDS population (Johansen et al., 2021) [62], where only 50 % (n = 9) of participants were satisfied with their sexual lives.

3.6.2. *Symptoms (S)*

All except one instrument (Johansen et al., 2021; [62] included symptoms as a factor although pain, fatigue, and emotional well-being were the only symptoms assessed. All but one study [59] assessed all three symptoms, with five [56-58,61,63] recording a negative association for each. Of the two remaining studies, pain in terms of Orofacial Pain was found to cause most impact on OHRQoL [59]. This study also measured aspects of mental well-being through the Orofacial Appearance and Psychosocial domains, where a third of participants reported feeling tense. Similar numbers found it difficult to relax. Contrary findings were reported by Bénistan at al., (2023) [57] with no impact noted for hEDS participants across domains for pain, fatigue, and emotional well-being. However, the results of these domains were omitted from this study. Consequently, it is unclear whether there was no impact or just low impact in these three SF-12 domains. Moreover, the SF-12 instrument used in this study is not recommended for small samples or as a mechanism to evaluate impact of individual domains [72].

3.6.3. *Individual Characteristics (IC)*

Instruments in three studies assessed the influence of IC (Table 7). Low QoL scores were reported for the Psychological and Social Relationship domains of the WHOQOL-BREF which include aspects of self-esteem, body image and relationships, related to the concept of IC. Negative associations with body image were also captured for mixed participants [59] where 25.3 % reported occasionally or often feeling uncomfortable and 15.3 % embarrassed. Dissatisfaction with employment and income were also measured through the Provision domain of the LiSAT-11 [62] where a small vEDS population indicated low fulfilment with occupational status. Factors associated with relationships were assessed in the same study through the Closeness domain but yielded no significant findings.

3.6.4. *Environmental Characteristics (EC)*

Rocchetti et al. [63] reported findings pertaining to EC through the Social Relationships and Environmental domains of the WHOQOL-BREF. The first included aspects of social support and the latter properties of freedom and security, access to care, opportunities for development and physical environment. Both domains recorded negative impact for a mixed EDS population with 82.73 % scoring below 70 for the Environment domain.

3.6.5. *General Health Perceptions (GHP)*

All but two studies [59,60] reported on perceptions of general health, all recording negative associations and one a significant impact ($p \leq 0.001$) compared to the control [56].

3.6.6. *QoL*

Four studies posed questions regarding overall satisfaction with QoL and reported an overall QoL score. Life satisfaction amongst vEDS participants [62] was just 45 %. Elsewhere, less than 30 % of a mixed cohort said their QoL was good or very good [63]. 15.9 % frequently found life less satisfying due to oral health [59], with the composite OHRQoL score calculated in this study substantially worse than population norms. Pain was also shown to impact on enjoyment of life for a hEDS population [60].

Table 3
Quality of Life Instruments employed across studies.

Acronym	Title	Type	No. of Items	Domains - No. and detail	Studies using instrument	Concept measured	Concept measured by author
BPI	Brief Pain Inventory (Short Form)	Generic	9	7 - General activity, Mood, Walking ability, Normal work, Relations with other persons, Sleep, Enjoyment of life	Bénistan & Martinez (2019)	Intensity and interference of pain	QoL
SF−12	Short-form 12 (health survey) questionnaire	Generic	12	8 - Physical Functioning, RLPH, RLEP, Vitality/fatigue, Emotional well-being, Social functioning, Pain, General health	Bénistan et al. (2023)	Health status	QoL
SF−36	The 36-item Short Form Health Survey (SF−36)/	Generic	36	8 - Physical Functioning, RLPH, RLEH, Vitality/fatigue, Emotional well-being, Social functioning, Pain, General health	Martinez et al. (2021) Colman et al. (2023)[1] Hakimi et al. (2023)[2]	Health status	HRQoL HRQoL QoL
LiSat−11	The Life Satisfaction Questionnaire	Generic	11	4 – Closeness, Health Leisure, Provision	Johansen et al. (2021)	Life satisfaction	QoL/ Life satisfaction
WHOQOL-BREF	World Health Organization Quality of Life - short version	Generic	26	4 - Physical health, Psychological, Social relationship, Environment	Rocchetti et al. 2021	QoL	QoL
OHIP−14	German short form of the Oral Health Impact Profile	Symptom specific	14	4 – Orofacial Pain, Orofacial Function, Orofacial Appearance. Psychosocial Appearance	Balke et al. 2023	Oral HRQoL	OHRQoL

Note. [1] Short-Form 36 health survey SF-36 (Dutch Version); [2] Medical Outcome Study Short Form (SF-36); RLPH = Role limitations due to Physical Health; RLEP = Role imitations due to Emotional Problems.

Table 4
Quality assessment using EPHPP tool for quantitative studies.

Study	Selection bias	Study design	Confounds	Blinding	Data Collection	Withdrawals/ Dropouts	Global Rating	Notes
Bénistan & Martinez, 2019	Moderate	Weak	N/A	Moderate	Strong	Moderate	Weak	QoL/ HRQoL secondary outcome. No control or comparison group. Small sample size. No reporting regarding existence or treatment of missing data.
Bénistan et al., 2023	Moderate	Moderate	N/A	Weak	Moderate	Weak	Weak	QoL/ HRQoL secondary outcome. No control/ comparison group. Inconsistencies in intervention and high percentage of protocol deviation. Reliability of SF−12 reduced with small sample and not recommended for evaluating individual domains SF−12 not reported. No reporting regarding existence or treatment of missing SF−12 data. Bonferroni corrections not completed in analysis requiring cautious interpretation of significance for secondary measures.
Balke et al., 2023	Moderate	Weak	Moderate	Moderate	Strong	N/A	Moderate	Large sample size. Full dataset. Predominantly hEDS population with small samples across other subgroups. No control. Comparisons made with population norms.
Colman et al., 2023	Moderate	Moderate	Strong	Moderate	Strong	Strong	Strong	QoL/ HRQoL secondary outcome. Small sample, powered for primary outcome not HRQoL measure.
Hakimi et al., 2031	Moderate	Moderate	N/A	Weak	Strong	Moderate	Weak	No control group. Small sample size. Possible issues with intervention integrity.
Rocchetti et al., 2021	Weak	Weak	Weak	Moderate	Strong	Moderate	Weak	No control group, (comparisons made with population norms). Low participation rate with possible bias for participants reporting psychological discomfort
Martinez et al., 2021	Moderate	Weak	Weak	Moderate	Strong	Moderate	Weak	No missing data. Control is non-symptomatic/ unaffected family members and comparison with population norms.
Johansen et al., 2021	Moderate	Weak	Strong	Moderate	Strong	Moderate	Moderate	Small EDS sample size. Missing data small and adjusted for. Control is population norms.

Table 5
Conceptual and methodological rigour.

Criteria	**Bénistan & Martinez** (BPI)	Bénistan et al. (SF-12)	**Balke et al.** (OHIP-14)	**Colman et al.** (SF-36)	**Hakimi et al.** (SF-36)	**Rocchetti et al.** (WHOQOL-BREF)	**Martinez et al.** (SF-36)	**Johansen et al.** (LiSat-11)
1. Did the investigators give a definition of quality of life?	X	X	X	X	X	X	X	X
2. Did the investigators state the domains they will measure as components of quality of life?	X	X	X	X	X	X	X	X
3. Did the investigators give reasons for choosing the instruments they used?	X	X	✓[1]	X	X	X	X	✓[2]
4. Did the investigators aggregate results from multiple items, domains, or instruments into a single composite score for quality of life?	X	X	✓	X	X	X	X	X
5. Were patients asked to give their own global rating for quality of life?	X	X	X	X	X	✓	X	✓
6. Was overall quality of life distinguished from health-related quality of life?	X	X	X	X	X	X	X	X
7. Were patients invited to supplement the items listed in the instruments offered by the investigators that they considered relevant for their quality of life?	X	X	X	X	X	X	X	X
8. If so, were these supplemental items incorporated into the final rating?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
9. Were patients allowed to indicate which items were personally important to them?	X	X	X	X	X	X	X	X
10. If so, were the importance ratings incorporated into the final rating?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rating	**0**	**0**	**25 %**	**0**	**0**	**12.5 %**	**0**	**25 %**

Note. [1] Use in previous studies with EDS population; [2] Broad measure compatible to the idea that living with hereditary thoracic aortic diseases may affect many aspects of people lives

3.7. HRQoL and EDS subtypes

Negative impact on HRQoL was recorded across all included subtypes. Findings pertinent to hEDS, cEDS and vEDS are listed in supplementary materials.

3.8. Moderating factors

All eight studies explored the possibility of moderating factors through analysis of interventions, subtypes or demographic variables or by reporting associated conditions.

Table 6
Instruments domains to Ferrans HRQoL concepts.

		Ferrans HRQoL concepts					
Study	**Instrument**	**IC**	**EC**	**Symptoms**	**FS**	**GHP**	**QoL**
Bénistan et al.	SF−12			1, 2, 3	4, 5, 6, 7	8	
Colman et al.	SF−36			1, 2, 3	4, 5, 6, 7	8	
Hakimi et al.	SF−36			1, 2, 3	4, 5, 6, 7	8	
Martinez et al.	SF−36			1, 2, 3	4, 5, 6, 7	8	
Bénistan & Martinez	BPI			9, 10	11, 12, 13, 14		15
Rocchetti et al.	WHO-QOL (BREF)	17, 18	18, 19	16, 17	16, 17, 18, 19,	20	21
Johansen et al.	LiSAT−11	22, 23	24		22, 23, 24, 25	25	26
Balke et al.	OHIP−14	28, 29		30, 28, 29	27, 29		
Total no. of domains across all instruments:		n = 6	n = 3	n = 19	n = 30	n = 6	n = 3

*Note.*SF-12/ SF-36 domains: Vitality / Fatigue^{1}, Emotional wellbeing^{2}, Pain^{3}, Physical functioning^{4}, RLPH^{5}, Social functioning^{6}, RLEP^{7}, General health^{8}
BPI domains: Sleep^{9}, Mood^{10}, Walking ability^{11}, Normal work^{12}, Relationships with others^{13}, General activity^{14}, Enjoyment of Life ^{15}
WHOQOL-BREF Physical Health^{16}, Psychological Health^{17}, Social Relationships^{18}, Environment^{19}
domains: (WHOQOL-Health Satisfaction^{20}), (WHOQOL-General QoL ^{21})
LiSat-11 domains: Provision^{22}, Closeness^{23}, Leisure^{24}, Health^{25}, (Life satisfaction question)^{26}
OHIP-14 domains: Oral Function^{27}, Orofacial Appearance^{28}, Psychosocial impact^{29}, Orofacial Pain^{30}

3.8.1. *Interventions*

Two studies explored the impact of interventions. Improved HRQoL was recorded immediately following a nine-week rehabilitation programme comprising physical, educational and mental well-being activities [58]. Pre- and post-intervention scores for Physical Function (38.9 ± 23.5/ 51.8 ± 21.8 p = .023) and RLEP (45.6 ± 43.3/ 70.2 ± 45.7 p = .038) indicate substantial impact on FS over six months (52.6 ± 22.7 p = .014). Conversely, a two-year study trialling compression garments [57] showed no effect on HRQOL.

3.8.2. *EDS subtype comparisons*

Across the studies comparing different subtypes (Table 8), one [63] indicated impaired QoL outcomes for participants with hEDS compared to cEDS in the WHOQOL-BREF Physical Health domain (mean difference 10.67, 95 % CI from −0.22 to −21.2), corresponding closely to both the HRQoL Symptoms and FS components. No significant difference between ten subtypes could be shown (p = 0.116) in the outcomes for OHRQoL [59]. In one study where participants with hEDS and HSD were included, no significant differences were found between the two populations [61].

3.8.3. *Symptomology*

Severe fatigue measured through a Visual Analog Scale and the Fatigue Severity Scale was found to be an associated factor in two studies with hEDS [60] or predominantly hEDS populations [57]. Contradictory indicators were found regarding the impact of pain. Bénistan & Martinez [60] found a link between the experiences of diffuse hyperalgesia in hEDS and reduced QoL. Pain was also seen to correlate negatively with each domain on the WHOQOL-BREF scale for mixed subtypes [61]: Psychological Health (r = -0.183, two-tailed p < 0.05), and with two-tailed p < 0.01, Physical Health (r = -0.501) Social Relationship (r = -0.417) Environment (r = -0.365). However, in a trial to measure the impact of using Compression Garments in a predominantly hEDS population [57], decreased pain ratings over a six-month period were not matched by enhanced QoL.

3.8.4. *Diagnosis factors*

Findings in two studies suggest diagnostic delay impacts HRQoL including significant impact on OHRQoL (p = 0.024) [61] and worse outcomes for the WHOQOL-BREF Psychological domain (HRQoL Symptom component) for participants awaiting diagnosis than against hEDS (mean difference −14.75, 95 % CI −28.91 to −0.60; p = 0.001) or cEDS (mean difference −19.74, 95 % CI −32.98 to −6.50; p = 0.001) populations [63]. However, one vEDS study [62] showed no significant impact from time since diagnosis on results.

3.8.5. *Comorbidities*

Three studies looked at the impact or association of comorbidity, with Balke et al. [61] finding a noticeable effect on OHRQoL (p = 0.008), and Rocchetti et al. [63] a negative correlation in all WHOQOL-BREF domains between QoL and Autism. A high correlation of both dysautonomia and gastro-intestinal symptoms were recorded in participants with hEDS [61].

3.8.6. *Demographics*

Three studies measured demographic variances as moderating factors. One found a noticeable effect of age on OHRQoL [59], (r = -0.19; 95 % CI −0.36 to −0.02; p = 0.027). Rocchetti et al. 11/06/2025 15:25:00 demonstrated a negative correlation between age and QoL but only related to EC (r = 0.205, two-tailed p < 0.01). Associations with high unemployment levels were recorded for a hEDS population [60] and a mixed cohort [62]. Conversely, in only one fifth of cEDS participants [56] was unemployment linked to health impairment.

4. Discussion

This systematic review sought to: i. examine what is known about the impact on HRQoL among adults living with EDS subsequent to the 2017 re-classification, ii. assess the impact of moderating factors, iii. afford insights into how HRQoL is captured and, iv. provide a critical appraisal of methodological quality. Literature search identified relatively few studies when assessed against inclusion criteria, with clarity regarding diagnostic status a factor. No qualitative studies met eligibility criteria. Consequently, while this review provides new insights into the factors that impact HRQoL for adults with of EDS, whether and how they are measured, it provides little additional understanding around the lived experience of HRQoL. Moreover, no inferences can be drawn in terms of the impact on HRQoL due to changes in diagnostic criteria.

Findings reflect what is known about HRQoL within the wider body of literature with synthesis demonstrating that, across many subtypes, EDS substantially impacts HRQoL. A review of quantitative studies dating back to 2000 [36] points to reduced levels of HRQoL compared to general populations. In this review, the domain most affected was that of physical role limitations as measured across multiple HRQoL instruments, reflecting the impact of Musculo-skeletal complaints and their association with dislocation and injury [25,34,73] on HRQoL. Evidence in this current review also highlights the effect on Functional Status (FS), namely physical and social functioning, participation in work, recreational activities and relationships, experiences reflected in earlier literature [26,29,30,73]. Similarly, poor perceptions of symptoms were captured across six studies, although limited by what is measured to pain, fatigue and emotional health, experiences reflected in

Table 7
Outcomes associated with impaired HRQoL.

	Individual Characteristics	Environmental Characteristics	Symptoms	Functional Status	General Health Perception	QoL
EPHPP: rated strong						
Colman et al. cEDS v Ctrl Median (IQR) Mean + /- SD			**P:** 57.5 [43] v 90 [10], < /= 0.001 **F:** 55 [25] v 70.00 [5] p < 0.002 **EW**: 68.00 [28] v 80 [16], p < 0.032	**PF**: 60 [40] v 100 [5] p < 0.001 **RLPH**: 75 (100) v 100 (0), p < 0.001 **SF:** 57.5 [45] v 90 [20], p ≤ 0.001	**GH:** 48.7 + /- 18.5 v 81.3 + /- 14.0, p ≤ 0.001	
EPHPP: rated moderate						
Balke et al.	**Orofacial Appearance:** 3.72 + / −2.32 25.3 % feeling self-conscious. **Psychosocial impact:** 15.3 % frequently feeling embarrassed		**Orofacial Pain:** most impact on OHRQoL, 4.26 + /- 2.28, p = 0.016 44.7 % frequent pain 36.9 % frequently uncomfortable when eating certain foods. **Orofacial Appearance:** 3.72 + /−2.32 33.2 % frequently tense **Psychosocial impact:** Least impact on OHRQoL, 1.92 ± 1.91 33.9 % difficult to relax	**Oral Function:** 2.56 + /- 2.31 57 % frequent interrupting meals 16.9 % frequent unsatisfactory diet 13.2 % frequently impaired taste 10.8 % frequently difficult to pronounce words. **Psychosocial impact:** 17.8 % irritable with other people 12.6 % difficulty with everyday tasks 5.4 % unable to do anything.		**Psychosocial impact:** Least impact on OHRQoL, 1.92 ± 1.91 15.9 % frequently feel life less satisfying. OHIP total score for all subtypes: 19.6 + /- 12.3
Johansen et al. Median score (quartiles) range	**Provision domain:** Employment 29 % satisfied			**(Closeness)** Sexual life: 4.5 (2.0) 1–6, 50 % satisfied	**Health:** Somatic Health: 4.0 (1.0) 2–6, 33 % satisfied.	**Life satisfaction:** 4.0 (1.0) 3–5, 45 % satisfied v 79 % (pop. norm)
EPHPP: rated weak						
Bénistan & Martinez			**Sleep:** 6.5 + /- 2.7 **Mood**: 5.5 + /- 3.2	**General Activity:** 7.4 + /- 2.1 **Normal work:** 7.9 + / −2.1 **Relationships with others:** 4.8 + /- 3.1		**Enjoyment of life:** 3.6 + /- 2.7
Bénistan et al.			**P:** 73.1 % impairing activities	**PF:** 58.2 % difficulty **RLPH:** 88.1 % impaired **RLEP:** 53.7 % impaired	**GH:** 67.2 % mediocre/poor	
Hakimi et al.			**P:** 35.5 + /- 18.6^{a} **P:** 34.6 + /- 20.3^{b} **F:** 20.5 + /- 13.5^{a} **F:** 24.7 + /- 15.6^{b} **EW**: 55.2 + /- 20.9^{a} **EW:** 56.6 + /- 23.9^{b}	**PF:** 37.1 + /- 23.2^{a} **PF:** 38.9 + /- 23.5^{b} **RLPH:** 10.5 + / −20.9^{a} **RLPH:** 19.7 + / −27.1^{b} **RLEP:** 54.4 + /−43.3^{a} **RLEP:** 45.6 + /−43.3^{b} **SF:** 38.2 + /- 18.9^{a} **SF:** 42.8 + /- 22.2^{b}	**GH:** 37.6 + /- 10.7^{a} **GH:** 38.9 + /- 12.9^{b}	
Rocchetti et al. Impaired QoL < 70 Severe impairment: at least 1 SD below the sample mean	**Psychological:** 55.05 + /−19.50 < 70: 71.22 % SI: 19.2 % **Social Relationships** 53.37 + /−24.24 < 70: 72.66 % SI: 19.2 %	**Social Relationships** 53.37 + /−24.24 < 70: 72.66 % SI: 19.2 **Environment:** 54.43 + /- 17.27 < 70: 82.73 % SI: 14.7 %	**Physical Health:** 45.56 + /−22.41 < 70: 81.4 % SI: 17.9 % **Psychological:** 55.05 + /−19.50 < 70: 71.22 % SI: 19.2 %	**Physical Health:** 45.56 + /−22.41 < 70: 81.4 % SI: 17.9 % **Social Relationships** 53.37 + /−24.24 < 70: 72.66 % SI: 19.2 % **Environment:** 54.43 + /- 17.27 < 70: 82.73 % SI: 14.7 % **Psychological:** 55.05 + /−19.50 < 70: 71.22 % SI: 19.2 %	**WHOQOL-Health satisfaction:** 2.46 + /- 1.00	**WHOQOL-General QoL(self-rated):** 3.00 + /−0.95
Martinez et al. hEDS v Population norms			**P:** 35.1 + /−23.4 v 75.2 + /−26.7, p < 0.001 **F:** 22.6 + /−1.3 v	**PF:** 45.7 + /- 27.2 v 84.2 + /−23.3, p < 0.001	**GH:** 28.5 + / −20.1 v 72.0 + / −20.3, p < 0.001	

(continued on next page)

Table 7 (*continued*)

	Individual Characteristics	Environmental Characteristics	Symptoms	Functional Status	General Health Perception	QoL
			60.9 + /−21.0, $p < 0.001$ **EW:** 60.0 + /−21.1 v 74.7 + /−18.0, $p < 0.001$	**RLPH:** 20.2 + /−34 v 81.0 + /−34.0, $p < 0.001$ **RLEP:** 49.9 + / −41.2 v 81.3 + / −33.3, $p < 0.001$ **SF:** 47.7 + /−27.3 v 83.3 + /- 22.7, $p < 0.001$		

Note. P = Pain; F = Fatigue; EW = Emotional Wellbeing; PF = Physical Functioning; RLPH = Role Limitations due to Physical Health; RLEP, Role Limitations due to Emotional Problems; SF = Social Functioning; GH = General Health; ADL = Activities of daily life; ^{a} = Measurement taken 9 weeks prior to intervention; ^{b} = measurement taken immediately prior to intervention

earlier literature [14,32]. However, although evidence weights impact towards FS and Symptoms, a similar concentration exists when comparing which elements of HRQoL are being measured. Across all studies, 83 % of the instrument domains assessed these two components. This weighting suggests findings reflect what is being measured rather than how HRQoL is experienced. This bias is problematic considering the outcomes in studies where IC was assessed, where two suggested detrimental impact due to perceptions of body image [59,63], another dissatisfaction around financial and occupational status [62]. Similarly, where EC was measured, negative outcomes suggest frustration with access to support and resources [63]. The experience of stigma associated with EDS is diverse and complex, connected both to living with a visible disability and an invisible condition [31,32,74]. Moreover, living with stigma is associated with withdrawal and depression [32,74] and shown to diminish QoL both in EDS populations [26] and in populations with chronic disease [75–77] more broadly. Similarly financial strictures have been linked to reduced HRQoL, limiting treatment [31] and placing a burden of self-care on many with EDS whose health needs are not met [78]. While more investigation into these concerns is needed, such issues evidence effects on HRQoL associated with IC and EC. Consequently, the instrument weightings towards FS and Symptoms serve to limit what is known, or not known about HRQoL for EDS populations. Such limitations have implications not just for studies undertaken post 2017 but also for the wider body of research into HRQoL and EDS.

The impact of such bias is further shown in findings related to moderating factors where three studies found evidence of the association [61,63] or impact [59] of comorbidity on HRQoL and two association with diagnostic delay [59,63]. Living with EDS is associated with a high incidence of comorbidity [18,78], a predictor for poor general health and physical functioning [79]. Similarly, the lengthy diagnostic journey experienced with EDS has been shown to be detrimental to physical and mental wellbeing [33]. Comorbidity and diagnostic delay are linked to poor HRQoL outcomes for rare diseases more generally, along with age, income, gender and time since diagnosis [45,80]. Indeed, across the HRQoL elements, evidence suggests that EC and IC have the strongest associations with HRQoL [41]. However, within the scope of our findings, investigation into the impact of these demographic factors on HRQoL is limited, in line with wider trends in HRQoL research [41,42]. Consequently, notwithstanding the polarising effects of how HRQoL is measured, the direction of HRQoL research places a further limitation on what is known about the impact of EDS, with the risk that important modifying factors also remain unreported.

Moreover, the tentative and contradictory findings in this study add further weight to evidence that questions the merit of prioritising HRQoL research around the impact of symptoms. While association between fatigue and poor HRQoL was noted for two predominantly hEDS populations [60,61], one study recorded a reduction in pain over a two-year period with no effect on scores for both FS and GHP [57]. Consequently, while broader evidence indicates a causal connection between severe symptoms and QoL in populations with chronic disease [42,75], there may be other influences at play. Objective measurements of pain through self-report can be problematic [69] and particularly in EDS populations where thresholds for pain are high [81] and factors such as personal motivation have demonstrated mitigating effects [27]. Moreover, considerable heterogeneity has been evidenced in how adults with EDS prioritise their symptoms [58]. Such findings further indicate the nuances influencing HRQoL in relation to EDS. Further investigation is needed to understand the elements important for HRQoL from the perspective of those living with the condition.

4.1. *How HRQoL is measured*

Substantial overlap in how each domain aligned across different HRQoL concepts was demonstrated. Three instruments contained at least one domain measuring more than one HRQoL concept, two contained four (Table 6). Of the six instruments employed, the OHIP-14 was the only one specified as a measure HRQoL, assessing four of the Ferrans et al. HRQoL concepts, and the WHOQOL-BREF the only one to address six. Across populations with EDS and other rare diseases, the SF-36 is the most used instrument for measuring HRQoL/QoL [36,42] despite being limited to just three HRQoL components and by other theoretical issues that question suitability. The SF-36 and other scales within this review measure FS in terms of an experience of loss or disablement, in contrast to an HRQoL model of optimization [40,82], where HRQoL is conceptualised as capacity for fulfilment. Moreover, in as much as HRQoL is a measure of perceived subjective wellbeing [39,40] then symptoms such as bodily pain are a determinant. Consequently, scales that aggregate symptoms as both determinant and element of HRQoL may serve to confuse HRQoL/QoL outcomes with their potential causes [38]. This is problematic for a population where pain and fatigue are widespread [6]. As such it is questionable how much can usefully be understood about QoL or HRQoL from the findings of these instruments.

Moreover, there is discrepancy between what each instrument pertains to measure and the concepts under investigation. Outcomes of studies using the SF-36 were presented as findings for both QoL and HRQoL (Table 3)., and the BPI used both as a measure of QoL [60] and a secondary measure for pain [58]. These inconsistencies highlight concerns over conceptual rigour (Table 5). No study included a definition of HRQoL or QoL or specified the components measured, deficits consistent with wider QoL research [83]. No measures provided opportunity for participants to prioritise items personally important to their perceived QoL [43]. Consequently, potential differences in perspective affecting those with chronic disease [45] are not captured.

4.2. *Assessment of methodological quality*

Five studies were assessed as weak, two moderate and one strong (Table 4), with issues of study design, confounding and binding of concern. Sample size was problematic, with studies often powered

Table 8
Outcomes associated with impaired HRQoL in studies comparing subtypes.

		hEDS	cEDS	vEDS	sEDS	Cl-EDS
Balke et al. EPHPP: rated moderate	IC	**Orofacial Appearance:** 3.70 + /−2.31) **Psychosocial impact:** 1.82 + /−1.83	**Orofacial Appearance:** 3.12 + /- 2.05) **Psychosocial impact:** 1.86 + /−2.08)	**Orofacial Appearance:** 2.83 + /- 2.26) **Psychosocial impact:** 2.00 + /−1.91		**Orofacial Appearance:** 4.86 + /−2.54) **Psychosocial impact:** 2.86 + /−2.48
	EC					
	S	**Orofacial Pain:** 4.30 + /−2.15) **Orofacial Appearance:** 3.70 + /−2.31) **Psychosocial impact:** 1.82 + /−1.83	**Orofacial Pain:** 3.83 + /−2.76) **Orofacial Appearance:** 3.12 + /- 2.05) **Psychosocial impact:** 1.86 + /−2.08)	**Orofacial Pain:** 3.17 + /−2.43 **Orofacial Appearance:** 2.83 + /- 2.26) **Psychosocial impact:** 2.00 + /−1.91		**Orofacial Pain:** 6.14 + /−2.27 **Orofacial Appearance:** 4.86 + /−2.54) **Psychosocial impact:** 2.86 + /−2.48
	FS	**Oral Function:** 2.59 + /- 2.26 **Psychosocial impact:** 1.82 + /−1.83	**Oral Function:** 2.41 + /- 2.40 **Psychosocial impact:** 1.86 + /−2.08)	**Oral Function:** 1.61 + /−2.17 **Psychosocial impact:** 2.00 + /−1.91		**Oral Function:** 3.29 + /- 1.98) **Psychosocial impact:** 2.86 + /−2.48
	GHP					
	QoL	OHIP−14 total score: 19.47 + /−11.97	OHIP−14 total score: 18.03 + /−12.93)	OHIP−14 total score: 15.17 + /−11.56)		OHIP−14 total score: 26.43 + /−12.83
Rocchetti et al. EPHPP: rated weak	IC	**Psychological:** 53.72 + /−20.01 < 70: 37 (78.7 %) SI: 10 (21.3 %) **Social Relationships** 50.71 + /−24.62) < 70: 35 (74.5 %) SI: 10 (21.3 %)	**Psychological:** 58.71 (17.70) < 70: 62 (69.7 %) SI: 12 (13.5 %) **Social Relationships** 57.12 + /−23.69) < 70: 62 (69.7 %) SI: 13 (14.6 %)	**Psychological:** 58.33 + /−20.83) < 70: 2 (66.7 %) SI: 0 **Social Relationships** 69.44 + /−4.81 < 70: 2 (66.7 %) SI: 0	**Psychological:** 38.97 (19.98) * p = 0.001 < 70: 14 (82.4 %) * p = 0.001 SI: 8 (47.1 %) * p = 0.018 **Social Relationships** 38.24 (21.66) * p = 0.013 < 70: 16 (94.1 %) SI: 7 (41.2 %)	
	EC	**Social Relationships** 50.71 + /−24.62) < 70: 35 (74.5 %) SI: 10 (21.3 %) **Environment:** 52.73 + /−17.20 < 70: 40 (85.1 %) SI: 11 (23.4 %)	**Social Relationships** 57.12 + /−23.69) < 70: 62 (69.7 %) SI: 13 (14.6 %) **Environment:** 56.74 + /- 17.18 < 70: 72 (80.9 %) SI: 7 (7.9 %)	**Social Relationships** 69.44 + /−4.81 < 70: 2 (66.7 %) SI: 0 **Environment:** 53.13 + /−5.41 < 70: 3 (100 %) SI: 0	**Social Relationships** 38.24 (21.66) * p = 0.013 < 70: 16 (94.1 %) SI: 7 (41.2 %) **Environment:** 47.24 + /- 17.85 < 70: 15 (88.2 %) SI: 5 (29.4 %)	
	S	**Physical Health:** 39.21 + /−20.06 * p = 0.004 < 70: 42 (89.4 %) SI: 14 (29.8 %) **Psychological:** 53.72 + /−20.01 < 70: 37 (78.7 %) SI: 10 (21.3 %)	**Physical Health:** 49.88 + /−22.11) < 70: 68 (76.4 %) SI: 8 (9.0 %) * p = 0.003 **Psychological:** 58.71 (17.70) < 70: 62 (69.7 %) SI: 12 (13.5 %)	**Physical Health:** 67.86 + /−28.57) < 70: 2 (66.7 %) SI: 0 **Psychological:** 58.33 + /−20.83) < 70: 2 (66.7 %) SI: 0	**Physical Health:** 45.56 + /−22.41 < 70: 15 (88.2 %) SI: 6 (35.3 %) **Psychological:** 38.97 (19.98) * p = 0.001 < 70: 14 (82.4 %) * p = 0.001 SI: 8 (47.1 %) * p = 0.018	
	FC	**Physical Health:** 39.21 + /−20.06 * p = 0.004 < 70: 42 (89.4 %) SI: 14 (29.8 %) **Social Relationships** 50.71 + /−24.62) < 70: 35 (74.5 %) SI: 10 **Environment:** 52.73 + /−17.20 < 70: 40 (85.1 %) SI: 11 (23.4 %) Psychological: 53.72 + /−20.01 < 70: 37 (78.7 %) SI: 10 (21.3 %)	**Physical Health:** 49.88 + /−22.11) < 70: 68 (76.4 %) SI: 8 (9.0 %) * p = 0.003 **Social Relationships** 57.12 + /−23.69) < 70: 62 (69.7 %) SI: 13 (14.6 %) **Environment:** 56.74 + /- 17.18 < 70: 72 (80.9 %) SI: 7 (7.9 %) Psychological: 58.71 (17.70) < 70: 62 (69.7 %) SI: 12 (13.5 %)	**Physical Health:** 67.86 + /−28.57) < 70: 2 (66.7 %) SI: 0 **Social Relationships** 69.44 + /−4.81 < 70: 2 (66.7 %) SI: 0 **Environment:** 53.13 + /−5.41 < 70: 3 (100 %) SI: 0 **Psychological:** 58.33 + /−20.83) < 70: 2 (66.7 %) SI: 0	**Physical Health:** 45.56 + /−22.41 < 70: 15 (88.2 %) SI: 6 (35.3 %) **Social Relationships** 38.24 (21.66) * p = 0.013 < 70: 16 (94.1 %) SI: 7 (41.2 %) **Environment:** 47.24 + /- 17.85 < 70: 15 (88.2 %) SI: 5 (29.4 %) Psychological: 38.97 (19.98) * p = 0.001 < 70: 14 (82.4 %) * p = 0.001 SI: 8 (47.1 %) * p = 0.018	
	GHP	**Health satisfaction:** 2.38 + /−1.05	**Health satisfaction:** 2.57 + /−1.00	**Health satisfaction:** 2.00 + /−1.00	**Health satisfaction:** 2.12 + /−0.78	
	QoL	**General QoL:** 2.98 + /−0.92	**General QoL:** 3.16 + /−0.95	**General QoL:** 2.33 + /−0.58	**General QoL:** 2.35 + /−0.79 * (p = 0.007)	

Note. hEDS = Hypermobile EDSD; cEDS = Classical EDS; vEDS = Vascular EDS; clEDS = Classical-like EDS; sEDS = Suspected EDS (awaiting diagnosed); IC = Individual Characteristics; EC = Environmental Characteristics; S = Symptoms; FS = Functional Status; GHP = General Health Perceptions; QoL = Quality of Life; ADL= activities of daily life; SI = Severe Impairment (measured at least 1 SD below the sample mean).

according to different intervention criteria. Moreover, studies failed to accommodate the unpredictability or progression of EDS symptoms [15], with six measuring outcomes at a single time point.

5. Recommendations for research

As evidenced in this review, nuanced examination of HRQoL amongst adults with EDS is scarce, highlighting the need for further research. More work is needed to understand how HRQoL is experienced and prioritised, alongside further investigation of moderating factors, in particular the impact of individual and environmental characteristics [41]. Areas of focus indicated in the findings of this review as well as elsewhere include family and social support [31], engagement with healthcare providers [26], access to resources, and experiences of stigma, as well as the impact of demographic factors such as age, treatment and comorbidity [79].

The lack of clarity around diagnostic classification is problematic for a condition with frequent reclassifications. Consequently, researchers should attempt to capture and communicate diagnostic information such as a date or type of diagnosis, to facilitate transparency and understanding.

More broadly, this study highlights a lack of conceptual and theoretical rigour around the use and measurement of both HRQoL and QoL. Future research should contain a pertinent definition of the HRQoL/QoL concepts intended to be measured. Moreover, none of the instruments employed in this review measured the impact of HRQoL equally across HRQoL components, all prioritising either Symptoms and/or Functional Status some measuring only three HRQoL elements, unlikely to capture the nuanced experiences of people with EDS. Consequently, it is also recommended that an EDS-specific tool be developed more accurately to measure HRQoL in this population.

6. Strength and limitations

This review is the first to synthesise knowledge around how HRQoL is impacted by EDS since the 2017 reclassification. The comprehensive and systematic search strategy is a strength of the review [84] although restrictions related to language potentially influence geographical concentration of the studies. However, the relatively small number of papers impact on the ability to draw any meaningful conclusions in relation to the change in diagnostic criteria. Furthermore, the EPHPP Quality Assessment tool was selected for appropriateness across heterogenous studies. However, criteria favour experimental research, weighted against cross-sectional design. Consequently, the quality of the six cross-sectional studies included in this review may be underrated.

7. Conclusion

Despite evidence of the negative impact on HRQoL, what is known about the experience of HRQoL for those living with EDS is limited. Understanding is hampered by a shortage of qualitative investigation, a lack of conceptual rigour and specifically a streamlined focus on the HRQoL components of symptoms and functional status, reflecting the limitations of the instruments used to measure both QoL and HRQoL. Given the limited treatment options, better understanding around how aspects of HRQoL are prioritised and experienced and how they can best be measured is urgently required, to ensure the effective management of this chronic and debilitating condition.

CRediT authorship contribution statement

Elaine Walklet: Writing – review & editing, Validation, Conceptualization. **Foster Joanna:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Danielle Stephens-Lewis:** Writing – review & editing, Validation, Conceptualization.

Ethics statement

No ethics approval is required for this systematic review manuscript

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.rare.2025.100107.

Data availability

Data will be made available on request.

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