Archives of Rehabilitation Research and Clinical Translation (2024) 6, 100360

ACRM AMERICAN CONGRESS OF REHABILITATION MEDICINE

Archives of Rehabilitation Research and Clinical Translation

Archives of Rehabilitation Research and Clinical Translation 2024;6:100360

Available online at www.sciencedirect.com

Review Article

The Effectiveness of Conservative Interventions on Pain, Function, and Quality of Life in Adults with Hypermobile Ehlers-Danlos Syndrome/ Hypermobility Spectrum Disorders and Shoulder Symptoms: A Systematic Review

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KEYWORDS
Compression orthoses;
Exercise;
Hypermobility;
Kinesiology tape;

Abstract *Objective:* To synthesize the evidence on conservative interventions for shoulder symptoms in hypermobile Ehlers-Danlos Syndrome (hEDS) and hypermobility spectrum disorder (HSD).
Data Sources: A literature search was conducted using data sources Medline, PEDro, CINAHL, AMED, Elsevier Scopus, and the Cochrane Library from January 1998 to June 2023.

List of abbreviations: ER, external rotation; hEDS, hypermobile Ehlers-Danlos syndrome; HRQoL, health-related quality of life; HSD, hypermobility spectrum disorder; KT, kinesiology tape; MDI, multidirectional instability; PSFS, Patient Specific Functional Scale; RCT, randomized controlled trial; SMD, standardized mean difference; TIDieR, Template for Intervention Description and Replication; WOSI, Western Ontario Shoulder Instability Index.

Disclosures: The authors declare the following potential conflict of interest with respect to the research, authorship, and/or publication of this article: B.L. is part of the authorship and has a study included in this review. B.L. did not perform risk of bias assessments for their own or any other studies included in this review. All other authors have no conflicts of interest to declare.
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Cite this article as: Arch Rehabil Res Clin Transl. 2024;6:100360

https://doi.org/10.1016/j.arrct.2024.100360

Physiotherapy;
Rehabilitation;
Shoulder;
Systematic review

Study Selection: The review included primary empirical research on adults diagnosed with hEDS or HSD who experienced pain and/or mechanical shoulder symptoms and underwent conservative interventions. Initially, 17,565 studies were identified, which decreased to 9668 after duplicate removal. After title and abstract screening by 2 independent authors, 9630 studies were excluded. The full texts of the remaining 38 were assessed and 34 were excluded, leaving 4 articles for examination.

Data Extraction: Two authors independently extracted data using a predefined extraction table. Quality assessment used the Joanna Briggs Institute checklists and the Template for Intervention Description and Replication.

Data Synthesis: The review covered 4 studies with a total of 7 conservative interventions, including exercise programs, kinesiology taping, and elasticized compression orthoses. Standardized mean differences were calculated to determine intervention effects over time. The duration of interventions ranged from 48 hours to 24 weeks, showing positive effect sizes over time in the Western Ontario Shoulder Instability Index, pain levels, improved function in activities of daily living, and isometric and isokinetic strength. Small to negligible effect sizes were found for kinesiophobia during completion of exercise programs.

Conclusions: Shoulder symptoms in hEDS/HSD are common, yet significant gaps in knowledge remain regarding conservative interventions, preventing optimal evidence-based application for clinicians. Further research is necessary to explore the most effective intervention types, frequencies, dosages, and delivery methods tailored to the specific requirements of this patient population.

Generalized joint hypermobility describes excessive movement beyond the normal range in multiple joints. It is estimated to affect 2%-57% of the population, and its prevalence is influenced by factors such as sex, race, and diagnostic criteria.[1-3] Generalized joint hypermobility can be advantageous in activities requiring flexibility such as some sports and the performing arts[4] but is also associated with clinical conditions such as hypermobile Ehlers-Danlos syndrome (hEDS) and hypermobility spectrum disorders (HSDs).[5] People with HSD may progress to hEDS over time, and the management and prognosis of disability for these conditions are comparable, suggesting the health care needs for individuals with hEDS and HSD are alike.[6] The prevalence of hEDS/HSD has been estimated to be 0.2%,[7] with reports of 3.4% of the general population describing chronic pain and hypermobility.[8] hEDS and HSD are heritable connective tissue disorders,[9] characterized by joint pain and hypermobility, soft tissue laxity, subluxations, and tissue fragility, leading to multisystemic symptoms.[10-12] People with hEDS/HSD frequently experience comorbidities because impaired connective tissue affects the gastrointestinal, cardiovascular, and autonomic nervous systems.[13] Furthermore, emerging research has proposed connections between hEDS/HSD and neurodivergence,[14,15] migraines, temporomandibular joint disorders, and impaired wound healing,[12] highlighting the systematic effect of connective tissue disorders. As such, the direct and indirect consequences of living with hEDS/HSD have been associated with a decreased ability to carry out activities of daily living and engagement in recreational physical activity,[12] poor health-related quality of life (HRQoL),[2] and increased anxiety and depression.[8,16]

The shoulder is particularly symptomatic in hEDS/HSD, with 84% reporting pain in this area.[17] The shoulder joint's inherent mobility predisposes it to instability and injury.[18] Thus, for individuals with hEDS/HSD, joint hypermobility further increases the vulnerability of the shoulder joint, which may lead to soft tissue injury, subluxation, and pain.[2,11,19] As a result, individuals with hEDS/HSD experience increased pain, fatigue, fear of movement, reduced shoulder function, and poorer HRQoL.[2,20] Even simple daily activities can cause shoulder instability,[21,22] leading to further limitations in physical activity.[11,20,23]

Despite the high prevalence of shoulder symptoms in hEDS/HSD, there is a lack of consensus on best clinical practices for treatment. Physiotherapists play a crucial role in managing joint instability in this population,[24] but clinical confidence in treating hEDS/HSD is limited.[25] The evidence on exercise therapy for shoulder symptoms in hEDS/HSD is still emerging, with recommendations focused on low-load stability exercises,[26] although their overall effectiveness is uncertain.[27] Strength training under close supervision has shown some benefits for the hypermobile shoulder.[28] However, strength training may not apply to all individuals across the hypermobility spectrum where symptoms and the degree of tissue laxity varies.[2]

With the increasing recognition and prevalence of hEDS/HSD, there is a growing rationale to investigate potential treatments and provide evidence-based recommendations for this population. This systematic review therefore aims to determine the effectiveness of conservative interventions for pain, function, and quality of life in adults who have hEDS/HSD and shoulder symptoms.

Methods

The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols guidelines[29,30] and was registered with the International Prospective Register of Systematic

Reviews (CRD42023411166). Ethical approval was obtained from Coventry University Ethics Committee on March 24, 2023 (P145212).

Data sources and search strategy

Together with 1 author (G.P.) trained in search strategy and systematic reviewing by the EPPI-Centre, a University librarian with experience of the medical sciences advised on the choice of electronic databases and construction of the search strategy. The databases chosen were CINAHL, MEDLINE, AMED (all using EBSCOhost), PEDro (Physiotherapy Evidence Database), Elsevier Scopus, and the Cochrane Library. The search incorporated Boolean logic (the words "AND" and "OR").[31] The searches were inclusive of articles published from January 1, 1998 (because the Villefranche nosology[32] and Brighton diagnostic criteria[33] were published after 1998) until June 9, 2023, after which the searches were transferred to EndNote. The searches were performed using key words and Medical Subject Headings adjusted to the specific database. Additionally, gray literature was searched to reduce publication bias[34] and reduce the risk of missing preliminary evidence.[35] This was carried out by searching the Electronic Theses Online Service and using the included publications to snowball search their reference lists and a Google Scholar forward citation search. The initial literature search was performed by 1 reviewer (A.H.). Search terms centered on synonyms relating to hEDS/HSD and the shoulder (table 1). Synonyms related to conservative treatment were not applied at the search phase of the review to ensure unknown types of treatment were included. Searches were imported and managed in Endnote X9,[a] which was used to remove duplicates. Covidence software[36,b] was used for the screening process, which allowed engagement between reviewers.

Table 1 Search terms and related synonyms used in the search strategy.

hEDS/HSD-related Search Terms	Shoulder-related Search Terms
hEDS	"Glenohumeral joint*"
HSD	"Upper extremit*"
Hypermobil*	"Upper limb*"
"Joint Instability"	Shoulder*
Laxit*	
Hyperflexib*	
Unstable	
"Ehlers-Danlos syndrome"	
Ehlers-Danlos III	
Ehlers-Danlos 3	
Ehlers-Danlos Type 3	
Ehlers-Danlos Type iii	
EDS-III	
EDS-3	
JHS	

Abbreviations: EDS, Ehlers-Danlos syndrome; hEDS, hypermobile Ehlers-Danlos syndrome; HSD, hypermobility spectrum disorder; JHS, joint hypermobility syndrome.
Note: * wildcard, multiple character searching.

Study selection

Inclusion and exclusion criteria (table 2) were based upon the literature review question formulation of Participants, Intervention, Comparison, Outcome, and study type.[37] The primary focus of the review was on adults (age $\geq$18y) with hEDS/HSD and shoulder symptoms. For the review, the term hEDS/HSD encompassed and included previous historical diagnoses of Ehlers-Danlos type III, joint hypermobility syndrome, and Ehlers-Danlos syndrome-hypermobility type. The Brighton diagnostic criteria for Villefranche Ehlers-Danlos syndrome-hypermobility type criteria,[32] joint hypermobility syndrome,[33] or the Ghent criteria for hEDS or HSD[10] must have been met.

Shoulder symptoms included pain and/or mechanical symptoms with a disruption in function of >3 months. Mechanical shoulder symptoms are related to a symptomatic extensive translation of the humeral head relative to the glenoid fossa[38] and present as instability, subluxations, and laxity.[2]

Conservative interventions were defined as interventions other than surgery, injections, and pharmacology. Conservative treatment consisted of single or multiple interventions applied directly to the shoulder. Any form of conservative treatment as an intervention for hEDS/HSD with shoulder symptoms was included. Interventions involving surgery, injections, or pharmacology were excluded. Interventions with any control group (ie, passive or active) or no control group (ie, single cohort studies with a before-after comparison) were included. Due to the strong evidence for people with hEDS/HSD and shoulder symptoms experiencing pain, functional issues, and poorer HRQoL, the primary outcomes of this systematic review were chosen accordingly. However, any study with other quantitative clinician-reported or patient-reported shoulder or upper limb-related outcomes related to decrements in health and defined under the umbrella term of "disability"[39] was included and categorized under secondary outcomes. The types of study included were randomized controlled trials (RCTs), case series, case control studies, and cohort studies published as full text in the English language. Single case studies, intervention protocols, and intervention development papers were excluded because of the lack of quantitative data.

After duplicate removal, the remaining articles were independently evaluated by 2 researchers (A.H. and L.S.) against the eligibility criteria to determine the appropriateness of titles, abstracts, and full-text articles. Any disagreements between the reviewers were discussed and agreed to by consensus.

Data extraction

From the included studies, the data were extracted independently by 2 reviewers (A.H. and L.S.) following a predefined extraction template. Two separate sets of tables were created by each reviewer and subsequently compared and merged into 1 set to maximize the accuracy of data extraction and analysis. The results extracted were relevant to the review question: study design, participant characteristics, methods used in analysis, intervention types, and outcome.[40] Any disagreements in data extraction were

Table 2 Inclusion and exclusion criteria.

Inclusion	Exclusion
Primary empirical research	Published before 1998
≥18 years	Not written in English
hEDS, HSD, JHS, Ehlers-Danlos syndrome hypermobility type	Not human participants
Shoulder symptoms: pain and/or mechanical symptoms	Not primary empirical research
Conservative treatment	Not about hEDS/HSD
Pain, function, HRQoL, Disability	Not about the shoulder
	Surgery, pharmacology, or injections
	Not examining outcomes of pain, function, HRQoL and disability

Abbreviations: hEDS, hypermobile Ehlers-Danlos syndrome; HRQoL, health-related quality of life; HSD, hypermobility spectrum disorder; JHS, joint hypermobility syndrome.

addressed between A.H. and L.S., with any conflicts discussed with a third reviewer until a consensus was reached.

The methodological bias in design, conduct, and analysis of the included studies was appraised using the Joanna Briggs Institute critical appraisal tools,[41] which offer checklists for appraising different types of studies. The appropriate checklist for each methodology was selected and used accordingly. Two reviewers (A.H. and L.S.) independently appraised the included studies, and discrepancies were discussed until consensus was reached. The Template for Intervention Description and Replication (TIDieR) checklist was used to extract detailed information about the interventions.[42]

Data analysis

SDs were estimated from standard errors or confidence intervals using accepted methods[43] with the assistance of a statistician. Due to the limited number of studies and the heterogeneity in study designs and outcome measures, a meta-analysis was inappropriate. However, the standardized mean difference (SMD, Cohen's *d*) was calculated for pre- to postintervention for each study arm. Change in outcome measures over time from baseline to end of treatment for each arm of each study was the focus, allowing for a comprehensive assessment of the outcomes achieved during the designated period as a representation of the overall effect of the intervention. Analysis at the end of treatment allowed for the point at which the maximal effect of the intervention could be seen. The utilization of SMDs allowed for the calculation of effect magnitude, thereby providing insights into the change in outcome measures after the application of the intervention in question.[44] The SMDs facilitated a comparative analysis across the studies and a comprehensive assessment of the various outcome measures employed. The statistical software Psychometrica[45,c] was used for these analyses, using the means and SDs for each group and outcome. The thresholds to interpret the SMD were 0.2=small effect, 0.5=medium effect, and 0.8=large effect.[46]

Results

Study selection

The search identified 17,565 records, and after duplicate removal, 11,256 records were exported to Covidence where a further 1588 duplicates were removed. Finally, 9668 titles and abstracts were screened for eligibility, and 9630 articles were excluded. Thirty-eight full-text articles were assessed for eligibility, and 4 were included in this systematic review. The study selection is presented in the PRISMA flow diagram (fig 1).

Study characteristics

The 4 included studies had a total of N=186 participants (87.63% female) (table 3).[47-50] The age of participants ranged from 18-65. The study of Chaléat-Valayer et al[47] included people diagnosed with hEDS and instability in 1 or both shoulders, leading to pain on the visual analog scale or disability. The instability criteria for Chaléat-Valayer et al[47] included recurrent dislocation or subluxation, occurring at least once a month or ≥12 times a year, although the study did not specify whether this information was obtained through patient reports, clinical examination, or both. Tudini et al[48] included people with diagnosed hEDS and self-reported symptoms or pain in the shoulder. The inclusion criteria of a study by Spanhove et al[49] were people with hEDS or HSD with confirmed multidirectional instability (MDI) through clinical examination, while Liaghat et al[50] included people diagnosed with HSD and self-reported symptoms or pain in the shoulder. Of the included studies, 2 were RCTs,[49,50] 1 was a pre-post study,[48] and 1 a quasi-experimental study.[47] All 4 papers had been published in a 3-year period and were conducted in France,[47] Denmark,[50] Belgium,[49] and the United States.[48] The participant follow-up periods were 48 hours,[47] 8 weeks,[46] 16 weeks,[49] and 24 weeks.[48] The studies employed diverse outcome measures; however, for the sake of this review and data consolidation, the relevant results included pain, function, kinesiophobia, and strength, with the latter 2 categorized under the broader term "disability." Kinesiophobia has been defined as an excessive, irrational, and debilitating fear of physical movement and activity resulting from a feeling of vulnerability because of a painful injury or reinjury.[51]

Conservative interventions

The 4 studies included in this systematic review examined 7 conservative treatment interventions for improving shoulder symptoms in patients with hEDS/HSD. Two studies examined exercise,[49,50] while the remaining studies looked at

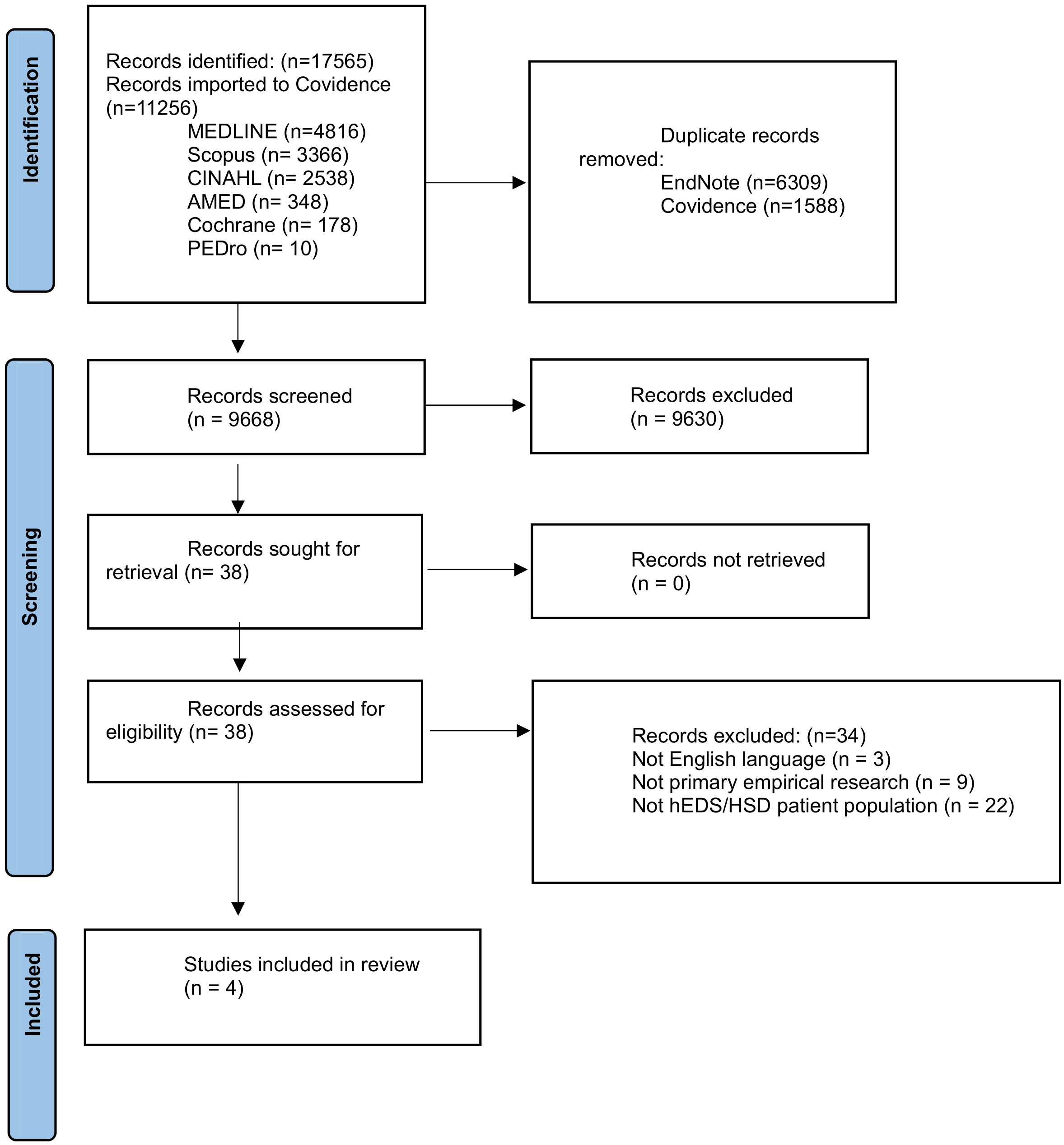

Fig 1 PRISMA flow diagram explaining the process of identifying and condensing articles based on inclusion and exclusion criteria. Abbreviations: hEDS; hypermobile Ehlers-Danlos syndrome; HSD, hypermobility spectrum disorder.

kinesiology tape (KT)[48] and an elasticized short sleeve compression jacket.[47] Within the exercise studies, Liaghat et al[50] undertook a comparison between high-load strengthening to low-load strengthening exercises. Meanwhile, Spanhove et al[49] evaluated the effectiveness of 2 home-based exercise programs. One program was individually tailored, incorporating the latest evidence for addressing shoulder instability in hEDS/HSD, while the other consisted of a standardized program based on evidence for MDI at the shoulder.[49] The KT study by Tudini et al[48] involved 2 groups, one receiving KT that crossed the glenohumeral joint line, and the other group receiving standard taping without crossing the glenohumeral joint line. Lastly, the compression orthoses study by Chaléat-Valayer et al[47] explored the effects of a short-sleeved, custom-fitted compressive jacket. The interventions were reported to varying degrees of detail (see appendix 1 and TIDieR checklist) and are summarized in table 4.

Critical appraisal

The critical appraisal is summarized in tables 5 and 6. The RCT conducted by Liaghat et al[50] was assessed as the most rigorous, based on the critical evaluation. This strength was attributed to the implementation of randomization and concealed allocation methods, ensuring baseline similarity between the groups. The transparency of the study was

Table 3 Data extraction table.

Author, Year Country	Study Design	Participant and Sample Characteristics	Intervention Details	Intervention Duration	Follow-up	Outcome Measures	Main Statistical Findings	Authors' Conclusions; Suggestions for Policy, Practice, and Research
Chaléat-Valayer et al[47] (2020) France	Quasi-experimental	N=46 participants: 10 lost to follow up (N=36 analyzed). hEDS. Multidirectional instability shoulder. Age: range 19-62y (mean 37.9±11.6y). Sex: 35 women (97.22%).	Wearing a short sleeved made to measure compressive jacket for 4wk followed by 4wk of not wearing the jacket.	8wk	None	Primary: Isokinetic strength of shoulder rotators (180°/s and 90°/s). Patient-reported outcome measures: SF-36 to assess quality of life. HAQ, FIS, QUEST, frequency. Shoulder instability, shoulder pain using VAS. Assessments: Baseline, 4 wk (day 28), and 8 wk (day 56).	At inclusion: SF-36: 30.4±5.9 for physical and 38.2±10 for mental. 25% patients not novo to compressive garments. Isokinetic test: Power external rotators 9.8W±8.5 at 180°/s and 9.7W±7.2 at 90°/s; internal rotators 120.9W(±20.2 at 180°/s and 19.8W± 19.8. Duration wearing compressive jacket 7.8±4.3h. QUEST: 4.1±0.7 for device subscale and 4.5±0.5 for service subscale. After 4 wk: Statistically significant increase external rotators by 1.29W (95% CI, 0.31-2.28) compared to without wearing (*P*=.0318); internal rotators increased by 2.3W (95% CI, 0.22-4.38) but no significant difference compared to without (*P*=.0620). No statistically significant effect on strength/power at 90°/s (*P*>.05). Joint stability: wearing jacket statistically significant decrease in subluxation (*P*=.0140) and dislocation (*P*=.0163) occurrence. Pain decreased from 3.5/10 to 2.5/10 but not statistically significant (*P*=.0964).	Compression garments increased power of external rotators and improved joint stability in high-speed movements, but 1 mo of jacket wearing brought no lasting effects to shoulder rotator power, so jacket needs to be kept on for benefits. Compression garments could be another aid to self-care.
Liaghat et al[50] (2022) Denmark	RCT	N=100 participants randomized: 50 each group. G-HSD or H-HSD. Shoulder symptoms. Age: range 18-65y. Mean age: HEAVY=38.6y; LIGHT=37y. Sex: 79 (79%) women.	Experimental group (Group A): High-load shoulder strengthening (HEAVY). Full range 2× wk supervised. Control group (Group B): Standard care (LIGHT). Low-load neutral to mid-range, 3× wk supervised.	16wk	1y	Primary: Shoulder function using WOSI. Secondary: self-reported PSFS, checklist Individual strength, subscale of fatigue, COOP/WONCA questionnaire, TSK, European Quality of life-5 Dimenensions-5-Level Scale, EQ-Visual Analogue, Global Perceived Effect on each of WOSI domains. Secondary objective outcome measures: Isometric shoulder strength in scaption internal and external rotation (using hand-held dynamometer), active and passive internal and external shoulder range of movement (using electronic goniometer), proprioception, shoulder laxity, hypermobility, and instability. Assessments: Before and after program.	ITT analysis: HEAVY greater improvement than LIGHT postintervention. (WOSI total, MD −174.5; 95% CI, −341.4 to 7.7), *P*<.05. Per-protocol analysis: Larger statistically significant effect favoring HEAVY. (WOSI total, MD −250.7; 95% CI, −323.4 to −178.0), *P*<.001.	High-load shoulder strengthening improved self-reported shoulder function, but the exercise program was associated with muscle soreness and headache. Further studies are required to assess the long-term effectiveness.

(*continued*)

Table 3 (*Continued*)

Author, Year Country	Study Design	Participant and Sample Characteristics	Intervention Details	Intervention Duration	Follow-up	Outcome Measures	Main Statistical Findings	Authors' Conclusions; Suggestions for Policy, Practice, and Research
Spanhove et al[49] (2022) Belgium	RCT	N=21 participants. hEDS/HSD. Multidirectional instability of shoulder. Age: range 18-65y. Median age: Group A=29y; Group B=33.5y (means not reported). Sex: 21 (100%) women.	Home-based exercise programs. Experimental group (Group A): Structured exercises based on recent research data. Control group (Group B): General exercise program based on evidence.	24wk	None	Shoulder instability (WOSI), upper extremity disability (using DASH), pain-related fear of movement (TSK), functional change (PSFS), patient perceived improvement (GROC), and pain pressure thresholds. Assessments: Baseline and 6, 12, and 24 wk.	Effect of time: Significant effect WOSI (P=.001) and DASH (P=.005), PSFS (P=.008), and GROC (P=.002). Effect of interaction: No significant effect WOSI (P=.69). No significant effects for TSK, DASH, PSFS, and GROC scores. Post hoc comparisons end of study comparted to baseline: DASH: P=.002, MD 8.6 points, 95% CI, 2.4-14.8; PSFS: P=.01, MD 4.3 points, 95% CI, 0.75-7.95. GROC significantly increased scores at end compared to 6 wk, P=.001, MD 1.02 points, 95% CI, 0.36-1.67. PPT: Upper trapezius significant interaction effect of treatment $\times$ time (P=.04). Post hoc within group B at end of study compared to baseline (P=.04; MD 1.23; 95% CI, 0.03-2.43), wk 6 (P=.005; MD 1.57; 95% CI, 0.37-2.77), wk 12 (P=.03; MD 1.32; 95% CI, 0.11-2.54). MD: WOSI 12 wk 240, end of study 325 points. DASH end of study compared to baseline: 8.6. PSFS end of study compared to baseline: 4.3 points. GROC end of study compared to wk 6: 1.02 points. No significant effect on TSK.	Both the experimental and control groups showed significant improvement in shoulder function, but a supervised multidisciplinary approach could be more beneficial for altering kinesiophobia in this patient population. Home exercises need to be performed regularly, below the pain threshold and with guided supervision.
Tudini et al[48] (2023) United States	Pre-Post with control	N=29 participants. hEDS. Bilateral shoulder pain. Age: Mean age 41.24± 16.4. Sex: 28 (96.55%) women.	Efficacy and short-term effects of 2 KT techniques: Experimental group (Group A) - 3 tapes crossing the GH joint line. Control group (Group B) - 3 tapes not crossing the GH joint line.	48h	Immediately 48h post treatment and then 48h post tape removal	Shoulder pain over the last 24h (current pain, average pain, and worst pain) using NPRS and function using the UEFI, WOSI, Quick DASH, and SPADI. Assessments: before and after study, and 48h posttreatment.	Effect of time: significant effect with UEFI, SPADI, QuickDASH, and WOSI (P<.001). NPRS over last 24h significant improvements (P=.005), improvements for worse pain over 24h (P<.001) and current pain (P=.023) Effect of interaction (difference between groups): no significant effect UEFI (P=.290), QuickDASH (P=.728), and WOSI (P<.132). SPADI not significant (P=.627). NPRS no significant effect (P=.802), for worst pain over 24h (P=.375) and current pain (P=.959). Significant differences between preintervention and immediate postintervention pain rating: MD=0.86, P=.026 and preintervention and 48h postintervention: MD=0.962, P=.782. No significant difference between postintervention and 48h postintervention pain ratings: MD=0.102, P=0.782.	No group difference. Significant reduction in UEFI, DASH, SPADI, WOSI, and NPRS. Future research looking at adding a true control group (no KT) and assessing proprioception.

NOTE. All data are reported as mean ± SD unless stated otherwise.

Abbreviations: CI, confidence interval; COOP/WONCA, Dartmouth Primary CareCooperative Research Network/World Organization of National Colleges, Academics and Academic Associations of General Practitioners/Family Physicians; DASH Disabilities of the Arm, Shoulder and Hand; FIS, Fatigue Impact Scale; GH, glenohumeral; G-HSD, Generalized Hypermobility Spectrum Disorder; GROC, Global Rating of Change; HAQ, Health Assessment Questionnaire; hEDS, hypermobile Ehlers-Danlos syndrome; H-HSD, Historical Hypermobility Spectrum Disorder; HSD, hypermobility spectrum disorder; ITT, intention-to-treat; KT, kinesiology tape; NPRS, numerical pain rating scale; PPT, Pain Pressure Threshold; PSFS, Patient Specific Functional Scale; QUEST, Quebec User Evaluation of Satisfaction with Assistive Technology; RCT, randomized controlled trial; SF-36, 36-Item Short Form Health Survey; SPADI, Shoulder Pain and Disability Index; TSK, Tampa Scale of Kinesiophobia; UEFI, Upper Extremity Functional Index; VAS, visual analog scale; WOSI, Western Ontario Shoulder Instability Index.

Table 4 TIDieR summary.

Variables	Study			
	Chaléat-Valayer et al[47] (2020)	Liaghat et al[50] (2022)	Spanhove et al[49] (2022)	Tudini et al[48] (2023)
1-Brief name of intervention	✔	✔	✔	✔
2-**WHY** (Underlying rationale, theory, or goal of essential elements)	✔	✔	✔	✔
3-**WHAT** (Materials used and where available)	✔	✔	✔	✔
4-**WHAT** (Procedures, activities, processes)	✔	✔	✔	✔
5-**WHO** Provided (qualifications, expertise, and training)	?	✔	?	✔
6-**HOW** (Mode of delivery)	✔	✔	✔	✔
7-**WHERE** (Types of location where intervention occurred and required infrastructure)	✔	✔	✔	✔
8-**WHEN & HOW MUCH** (number, schedule, duration, intensity, dose of intervention)	✔	✔	✔	✔
9-**TAILORING** (if intended to personalized, titrated, or adapted, describe)	✔	✔	✔	✔
10-**MODIFICATIONS** (if modified during study, describe the changes)	✔	✔	✔	?
11-**HOW WELL (Planned)** (describe if adherence or fidelity assessed, as well as how and what strategies used)	✔	✔	✔	✔
12-**HOW WELL (Actual)** (if adherence or fidelity assessed, describe how well intervention was delivered as planned)	✔	✔	✔	✔

NOTE. ✔=Yes, ✘=NO, ?=unsure.

Table 5 Critical appraisal using JBI for randomized controlled trials.

JBI criteria: RCT	Study Authors		
	Liaghat et al[50] (2022)	Spanhove et al[49] (2022)	Tudini et al[48] (2023) (Pre-Post Study)
1. Random allocation	✔	✔	✔
2. Concealed allocation	✔	✔	✔
3. Baseline similarity	✔	✔	✘
4. Blinding of participants	✔	✔	✔
5. Blinding of therapists	✘	✘	✘
6. Blinding of assessors	✔	?	?
7. Treatment groups treated similarly other than the intervention	✔	✔	✔
8. Between groups statistical analysis	✔	✔	✔
9. Intention-to-treat analysis	✔	✘	✘
10. Outcomes measured same way	✔	✔	✔
11. Outcomes measured in reliable way	✔	✔	✔
12. Appropriate statistical analysis	✔	✔	✔
13. Trial design appropriate and if deviations accounted for in analysis	✔	✔	?

NOTE.✔=Yes, ✘=No, ?=Unclear.
Abbreviations: JBI, Joanna Briggs Institute; RCT, randomized controlled trial.

enhanced by the blinding of assessors and the disclosure of trial information without revealing the hypothesis direction. The study's robustness was reinforced using intention-to-treat analysis and appropriate statistical methods. During the per-protocol analysis, 16 participants were omitted from the HEAVY group and 17 from the LIGHT group because of poor adherence. In Spanhove et al,[49] the unclear status of intention-to-treat analysis introduced some uncertainty, but the study demonstrated a decreased risk of bias through its comprehensive statistical analysis and efforts to ensure consistent and reliable outcome measurements. The quasi-experimental study by Chaléat-Valayer et al[47] exhibited a lack of baseline parity among participant groups and potential biases because participants acted as their own control. On the other hand, Tudini et al[48] mitigated many biases associated with a pre-post study by employing strategies such as randomization and blinding of participants and ensuring participant retention, although the reliability of the outcome measurements remains unclear.

Table 6 Critical appraisal using JBI for quasi-experimental study.

JBI Criteria Quasi-Experimental	Study Chaléat-Valayer et al[47] (2020)
1. Clear differentiation between cause and effect. Which variable comes first	✔
2. Participants in comparisons similar	✘
3. Baseline similarity	✘
4. Control group	Own control
5. Multiple measurements of outcome both pre- and postintervention	✘
6. Follow up complete and if not, differences described and analyzed	✔
7. Outcomes in any comparisons measured the same	✔
8. Outcomes measured in reliable way	?
9. Appropriate statistical analysis	✔

NOTE. ✔=Yes, ✘=No, ?=Unclear.
Abbreviation: JBI, Joanna Briggs Institute.

Analysis of results

To calculate the SMDs, the experimental group and control group in each study were categorized as interventions, denoted as intervention A and intervention B. This categorization was necessitated by the fact that in 3 of the studies,[48-50] the participants in the control group still underwent an active treatment. Given the focus of the review was on conservative interventions, all groups were therefore classified as active treatment groups. The results obtained from the SMD analysis are presented in table 7, with the primary analysis conducted at the end of treatment for each respective group. In the case of Spanhove et al,[49] this endpoint for treatment was taken as 12 weeks as we deemed it closer to the endpoint of Liaghat et al[50] at 16 weeks. To gain a comprehensive examination of the treatment effects of a home-based exercise program,[49] additional SMDs were calculated at 24 weeks, the results of which are detailed in appendix 2, contributing valuable insights into the mid-term effect of home-based exercise programs beyond the primary treatment phase. Liaghat et al[52] showed data for a 1-year follow-up, which was narratively discussed.

The SMD analysis results using the Western Ontario Shoulder Instability Index (WOSI) exhibited large effect sizes for 2 of the studies[49,50] in intervention A and a medium effect size for intervention B, as illustrated. One study[48] demonstrated large effect sizes for WOSI in both intervention groups. Pain outcome analyses revealed large effect sizes for both interventions in one study,[50] while another study[48] showed a small effect size for intervention A and a medium effect size for intervention B. There were negligible effect sizes for kinesiophobia in both intervention groups in Spanhove et al,[49] while Liaghat et al[50] identified a small effect size in group A. Positive effect sizes in functional outcomes were observed with the Patient Specific Functional Scale (PSFS[49,50]) and the Upper Extremity Functional Index.[48] Liaghat et al[50] demonstrated medium effect sizes for both interventions with the PSFS, while Spanhove[49] exhibited a small effect size for intervention A and a medium effect size for intervention B. Tudini et al[48] revealed a medium effect size for intervention A and a small effect size for intervention B with the Upper Extremity Functional Index. In the 16-week strengthening program emphasizing full range of movement and high loads targeting the external rotators of the shoulder (intervention A),[50] there was a small effect size for isometric external rotation (ER), while compression orthoses[47] had a small effect size for mean isokinetic power of ER at 180°/s. All other strength measurements for both studies in both groups showed negligible SMDs.

In the compression orthoses study,[47] the authors documented a reduction in pain on the visual analog scale rating from 3.5/10 to 2.5/10 after 4 weeks of jacket wear, although statistical significance was not achieved (P=.0964). Additionally, there was a statistically significant decrease in the occurrence of joint instability episodes, with 72% of participants experiencing such events after wearing the jacket compared to 92% without the jacket after 4 weeks (P=.0326).[47] As previously discussed, the evaluation of pain and joint instability occurred at the 4-week point, immediately following jacket wear, and then again 4 weeks later without the jacket, with no baseline measurements taken. Consequently, the inability to calculate SMDs as part of the current systematic review is attributed to this study design.

Discussion

This review aimed to present the available research on conservative interventions for shoulder symptoms in people living with hEDS/HSD. From the SMD results obtained, varying degrees of effect size are presented across all the interventions ranging from negligible to large, which may in part be because of the heterogeneity in the studies in terms of intervention type, outcome assessed, and duration of treatment. However, the SMDs offer valuable insights into the effects of conservative interventions on pain, function, disability, and quality of life in individuals with hEDS/HSD experiencing shoulder symptoms.

The findings of the review highlight the role that low-load and high-load exercise holds in the rehabilitation process for this patient population, with positive effect sizes for the WOSI, pain, and functional activities of daily living. This data further contributed to the evidence required to justify the overall effectiveness of rehabilitation for this patient group.[27] Furthermore, this review provides insights into the importance of strength exercises[50] on pain, shoulder

Table 7 Standardized mean differences (Cohen's *d*) — WOSI, pain, kinesiophobia, and function.

Outcome	Author, Year	Intervention (A) Pre Mean ± SD	Intervention (A) Post Mean ± SD	Cohen's *d*	95% CI	Intervention (B) Pre Mean ± SD	Intervention (B) Post Mean ± SD	Cohen's *d*	95% CI
WOSI	Liaghat,[50] 2022	1042.1±351.9	606.9±384.7	−1.18 Large	−1.781 to −0.58	1071.5±379.8	802.6±419.8	−0.64 Medium	−1.242 to −0.0102
	Spanhove,[49] 2022	1330±271.6	955±238.6	−1.47 Large	−2.798 to −0.136	1155±336.3	933±454.8	−0.56 Medium	−1.818 to −0.708
	Tudini,[48] 2023	1248.64±404.86	684.3±479.8	−1.27 Large	−2.42 to −0.123	1127±385.18	740.2±382	−1.01 Large	−2.083 to −0.066
Pain	Liaghat,[50] 2022	3.88±2.1	1.70±2.1	−1.04 Large	−1.631 to −0.449	4.08±2.2	2.26±2.2	−0.83 Large	−1.403 to −0.248
	Tudini,[48] 2023	3.5±2.53	2.64±2.34	−0.35 Small	−1.409 to −0.703	3.53±1.89	2.47±2.1	−0.53 Medium	−1.56 to 0.499
Kinesiophobia	Liaghat,[50] 2022	22.1±5.79	20.45±5.81	−0.28 Small	−0.841 to 0.273	23.38±5.23	22.23±6.53	−0.19 Negligible	−0.75 to 0.3661
	Spanhove,[49] 2022	40±7.8	39±9.1	−0.12 Negligible	−1.301 to 1.065	40±9.5	39±6.5	−0.12 Negligible	−1.364 to 1.118
Function	Liaghat,[50] 2022	3.89±1.74	5.73±2.8	0.79 Medium	0.214-1.365	3.91±2.11	5.55±2.8	0.66 Medium	0.093-1.232
	Spanhove,[49] 2022	10±4.4	11±3.4	0.25 Small	−0.932 to 1.441	13±4	16±3.7	0.78 Medium	−0.507 to 2.064
	Tudini,[48] 2023	44.86±19.51	55.08±20.6	0.51 Medium	−0.555 to 1.574	51.33±14.75	58.13±14	0.47 Small	−0.555 to 1.497
Isokinetic strength	Chaléat-Valayer,[47] 2020								
IR 90°/s		19.8±19.8	20.5±18	0.04 Negligible	−0.616 to 0.69	19.8±19.8	19.7±18.1	−0.01 Negligible	−0.659 to 0.648
IR 180°/s		20.9±20.2	23.3±20.9	0.12 Negligible	−0.537 to 0.771	20.9±20.2	22.1±19.4	0.06 Negligible	−0.593 to 0.714
ER 90°/s		9.7±7.2	10.3±7.5	0.08 Negligible	−0.527 to 0.735	9.7±7.2	9.5±8.1	−0.03 Negligible	0.679-0.627
ER 180°/s		9.8±8.5	11.4±9.5	0.18 Small	−0.477 to 0.832	9.8±8.5	10.1±8.6	0.04 Negligible	−0.618 to 0.688
Isometric strength	Liaghat,[50] 2022								
IR		0.4±1.6	0.1±0.2	−0.29 Negative	−0.846 to 0.269	0.33±1.5	0.37±1.7	0.03 Negligible	−0.529 to 0.579
ER		0.2±0.11	0.3±0.1	0.36 Small	−0.287 to 0.827	0.2±0.1	0.2±0.9	0.01 Negligible	−0.549 to 0.559

NOTE. For the purpose of the review, the experimental group is represented as Intervention A, and the control group is represented as Intervention B. Standardized mean difference: 0.2=small effect; 0.5=medium effect; 0.8=large effect.
Abbreviations: CI, confidence interval; IR, internal rotation; ER, external rotation; WOSI, Western Ontario Shoulder Instability Index.

function, HRQoL, and kinesiophobia and of home-based exercise[49] on shoulder function and HRQoL. However, it emphasizes the importance of considering the delivery method and level of supervision required for individuals with hEDS/HSD and shoulder symptoms. In the 16-week trial conducted by Liaghat et al,[50] the 2 intervention groups differed in supervision levels, with the HEAVY group supervised twice a week and encouraged to self-train once a week, while the LIGHT group self-trained 3 times a week but received supervision at weeks 5 and 11 when new exercises were introduced. In the 6-month trial by Spanhove et al,[49] the participants received either a program that was designed on recent research on the management of hEDS/HSD or a program that was evidence-based for MDI of the shoulder. Both programs were closely monitored and adjusted based on participant feedback, investigating the most advantageous type, frequency, dosage, or delivery method that is safe for such a fragile patient population.[53] The positive SMDs observed may be attributed to the careful management of each intervention group participating in the home-based exercise programs, which provides a method of monitoring and ensuring accountability. Similarly, Liaghat et al[50] supervised both intervention groups in their study, recognizing that patients with hEDS/HSD may have decreased tissue stiffness[54] and difficulties performing strengthening exercises unsupervised.[50] Therefore, supervision by a therapist may have allowed for better management of potential adverse events and load progression.[50] However, while supervised exercise and self-training are equally effective for shoulder conditions,[55] this evidence does not specifically address hEDS/HSD, where mechanical shoulder symptoms such as subluxation or instability are highly prevalent.[19]

Spanhove et al[49] also shed light on the comorbidities and challenges faced by individuals with hEDS/HSD such as fatigue[56] and dysautonomia,[57,58] which may hinder their ability to attend appointments in person. The study by Spanhove et al[49] underscores the significance of facilitating home-based exercise programs, proposing that individuals with hEDS/HSD can experience functional improvements through monitored home-based exercise regimes conducted in a consistent and comfortable environment. The findings of the review highlight the potential benefit of strength exercises and home-based programs in managing shoulder symptoms in individuals with hEDS/HSD. Further research is warranted to explore optimal intervention types, frequencies, dosages, and delivery methods tailored to the needs of this patient population.

The SMDs from kinesiophobia draw attention to the importance of considering how fear of movement may be improved in individuals with hEDS/HSD when exercising. SMDs from the Spanhove et al[49] results exhibited negligible effect sizes for both groups. However, a supervised approach is more effective in improving kinesiophobia in hEDS/HSD.[49] Previous research also contributes to the reported associations between hEDS/HSD and fear of movement, emphasizing the need for further investigation into the complexities of this phenomenon within the hEDS/HSD context[59] and that significant reductions in kinesiophobia can be found when a multidisciplinary team is utilized.[60,61] While there is potential efficacy observed in both low-load and high-load exercises, as well as in the delivery methods of these exercises, additional research is required to identify the optimal frequency, intensity, duration, and specific types of resistance exercise suitable for individuals with hEDS/HSD to engage in independent exercise without posing a fear of injury. Addressing the fear of movement in this patient population is crucial to enabling the emerging benefits of exercise while mitigating the risk of injury.[59] This fear and risk of injury underscore the importance of designing future studies focused on refining exercise parameters for people living with hEDS/HSD.

The review highlights emerging evidence supporting the positive effect of KT[48] and compression orthoses[47] on individuals with hEDS/HSD experiencing shoulder symptoms. Although the short follow-up periods within these 2 studies limit conclusive findings, the SMD calculations suggest a reduction in pain and improvement in function/WOSI with the utilization of KT.[48] Mechanically, the positive effects of KT were attributed to improved proprioception; however, proprioceptive outcomes were not measured in the work by Tudini et al.[48] As such, further research is warranted to explore the underlying mechanisms, optimal application techniques, and duration of use for this treatment modality.

The study on the use of compression orthoses[47] had methodological deficiencies. These shortcomings include limited reporting of pain and instability outcomes, absence of follow-up data regarding baseline patient-reported outcome measures, and reliance solely on pre-post intervention data, which focused on strength. The authors[47] attribute the exclusion of baseline data from the 36-Item Short Form Survey Instrument, Health Assessment Questionnaire, and Fatigue Impact Scale because of the wide variation at baseline of the sample population and their utilization of compression orthoses before the study. Despite this, compression orthoses did yield small effect size for isokinetic mean power at 180°/s ER, suggesting a potential beneficial impact of the compression orthosis at the end range of movement, possibly through proprioceptive feedback.[47] This feedback may contribute to increased joint stability in end-range positions, where hypermobile joints typically exhibit diminished stability.[62] Despite the small effect sizes, these findings yield valuable insights into the use of compression in individuals with hEDS/HSD experiencing shoulder symptoms. Future research is required to explore the specific ranges of movement that individuals with hEDS/HSD require for optimal stability enhancements to facilitate functional abilities. Additionally, careful consideration should be given to determining the most effective approaches for addressing and improving these stability gains.

Mid- and long-term follow-ups

At 24 weeks, Spanhove et al[49] demonstrated that both interventions A and B had large effect SMDs from pre- to post-treatment in WOSI scores as well as an increase from small to large effect size in intervention A in function (PSFS). Additionally, kinesiophobia increased from negligible effect size to a small effect size in both groups, indicating a positive change. The 1-year follow-up findings by Liaghat et al[52] revealed continued maintenance of improved WOSI scores for both intervention groups, with a promising outcome indicating a favorable impact on emotional wellbeing attributed to the HEAVY strength program. These results suggest that future research should focus on identifying studies with extended time frames and give due consideration to the outcomes of HRQoL and kinesiophobia in individuals with hEDS/HSD.

Study strengths, limitations, and future directions

The findings of this review indicate the importance of carefully considering specific conservative interventions and their effect on various health aspects in individuals with hEDS/HSD, though based on a limited number of studies. An additional search of the selected databases between June 9, 2023 and July 1, 2024 identified no further relevant records, demonstrating that the review provides adequate coverage of the most up-to-date scientific evidence. The review identified that low-load and high-load strengthening exercises, KT, and compression orthoses demonstrate potential effectiveness in alleviating pain, enhancing shoulder strength, improving shoulder function, and enhancing HRQoL. The lack of studies, variability in follow-up time frames, and the different outcome measures used in the studies meant that a meta-analysis could not be undertaken. However, where possible, SMDs were calculated to inform the narrative analysis. For the purpose of this review, each arm of each study was considered as an intervention group rather than a control group because all participants received a form of active conservative treatment.

While this review offers important insight into the conservative management of shoulder symptoms in hEDS/HSD, it is not without limitations. First, half of the studies examined were not RCTs and therefore lacked appropriate control groups for comparison. Furthermore, our findings are somewhat constrained by the limited number of eligible studies available for analysis, leaving only a modest body of evidence from which to draw conclusions. However, this is more of a reflection of the current literature and was useful to inform the review and future research recommendations. While this review primarily focused on adults, future work should consider the effectiveness of conservative interventions in pediatric populations and the importance of early management of a lifelong condition. The recent advancements in the diagnostic framework for pediatric hypermobility lay a crucial groundwork for enhancing clinical care and management strategies for children and those under the age of 18.[63]

Conclusions

To our knowledge, this is the first systematic review to evaluate the available literature regarding the effectiveness of conservative interventions in hEDS/HSD patients with shoulder symptoms. By consolidating the available research, we have attempted to enhance the understanding of conservative management for this patient population. The review includes 4 studies and suggests potential benefits from conservative management programs that integrate low-load and high-load strengthening regimes, KT, and compression orthoses. These findings highlight the effectiveness of strengthening exercises in improving function, reducing pain, and enhancing strength, although the necessity for supervision during these exercises remains a critical consideration with this patient population. However, significant knowledge gaps hinder optimal evidence-based application, with limited evidence evaluating the efficacy of KT and compression garments. As such, this review underscores the need for additional research with a focus on outcomes important to people living with hEDS/HSD, such as kinesiophobia and improving functional capabilities relevant to everyday life. It also highlights the need to develop a comprehensive treatment package for individuals with hEDS/HSD and shoulder symptoms.

Suppliers

a. Endnote X9; Clarivate.
b. Covidence systematic review software; Veritas Health Innovation.
c. Psychometrica; Dr. Alexandra Lenhard.

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Acknowledgments

The authors thank Yamuna Dass, Statistician, Coventry University, for their expertise and assistance with the statistical support that was provided and Chris Bark, at Coventry University, for their invaluable expertise with the searches.

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