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Short-term effectiveness of high-load compared with low-load strengthening exercise on self-reported function in patients with hypermobile shoulders: a randomised controlled trial

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ABSTRACT

Objectives To investigate the short-term effectiveness of high-load versus low-load strengthening exercise on self-reported function in patients with hypermobility spectrum disorder (HSD) and shoulder symptoms.

Methods A superiority, parallel-group, randomised trial (balanced block randomisation, electronic concealment) including adult patients (n=100) from primary care with HSD and shoulder pain and/or shoulder instability ≥3 months. Patients received 16 weeks of shoulder exercises (three sessions/week): HEAVY (n=50, full-range, high-load, supervised twice/week) or LIGHT (n=50, neutral/mid-range, low-load, supervised three times). The primary outcome was the 16-week between-group difference in self-reported function measured with the Western Ontario Shoulder Instability Index (WOSI, scale 0–2100, 0=best, minimal important difference 252 points). Secondary outcomes were self-reported measures including quality of life and clinical tests including shoulder muscle strength and range of motion. An intention-to-treat analysis with multiple imputation was conducted by a blinded biostatistician using linear regression.

Results 93 of 100 patients (93%) completed the 16-week evaluation. The mean WOSI score between-group difference significantly favoured HEAVY (−174.5 points, 95% CI −341.4 to −7.7, adjusted for age, sex, baseline score, clustering around clinic). The secondary outcomes were inconclusive, but patients in HEAVY were less likely to have a positive shoulder rotation test >180°, and more likely to rate an important improvement in physical symptoms. There were no serious adverse events, but HEAVY was associated with more transient muscle soreness (56% vs 37%) and headaches (40% vs 20%).

Conclusion High-load shoulder strengthening exercise was statistically superior to low-load strengthening exercise for self-reported function at 16 weeks and may be used in primary care to treat patients with HSD and shoulder pain and/or instability to improve shoulder function in the short term. Further studies are needed to confirm the clinical relevance, and patients should be supported to manage associated minor adverse events.

Trial registration number NCT03869307.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Four out of five patients with hypermobility spectrum disorder (HSD) experience symptoms in the shoulder joint. However, evidence for treatment is sparse.

WHAT THIS STUDY ADDS

⇒ For patients with HSD and shoulder pain and/or shoulder instability in primary care, a supervised, progressive high-load shoulder strengthening exercise programme (full-range, open kinetic chain) resulted in greater self-reported improvements in shoulder function than less supervised and less progressive low-load exercises (neutral to midrange) at 16 weeks.

⇒ More than two-thirds of patients receiving high-load strengthening exercise improved shoulder function above the threshold for minimal important difference, and 64% reported an important improvement in physical symptoms postintervention. The exercise programme was associated with transient muscle soreness and headache.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ The high-load shoulder strengthening exercise programme may be used in patients with HSD and shoulder symptoms in primary care to improve function and reduce shoulder symptoms in the short term.

⇒ Further studies are needed to confirm the clinical relevance and the long-term effectiveness. Clinicians should pay attention to and help manage associated minor adverse events.

INTRODUCTION

Joint hypermobility is defined as the ability to move the joints beyond the normal range of motion, with an estimated prevalence of 2%–57%, depending on race, sex and diagnostic criteria.[1 2] Joint hypermobility may be advantageous in activities and sports where high flexibility is required.[3] However, it may be symptomatic with, for example, chronic/recurrent pain, joint instability, musculoskeletal complaints, fatigue and disability, resulting in decreased ability to participate in daily activities, increased psychological problems and poor health-related quality of life. [3–7] This symptomatic clinical entity is termed hypermobility spectrum disorder (HSD).[8]

Remarkably, four out of five people with HSD experience symptoms in the shoulder joint[3 9–11] with profound consequences in daily life.[4 5] Recent studies have reported altered scapular kinematics, imbalanced electromyographic scapular muscle activity and increased humeral head translation in patients with HSD and multidirectional shoulder instability.[12 13] However, there is no gold standard management, and no studies have focused on treatments of the shoulder for this patient group.[14–17] Generally, an important and effective component of exercise interventions for persistent shoulder complaints—such as rotator cuff tendinopathy and anterior or multidirectional glenohumeral instability—aims to improve the function of the scapular stabilising muscles and rotator cuff muscles.[18–20] Furthermore, high-load strengthening exercise has proven to be particularly effective in increasing muscle strength of the global muscles and stiffness of the tendons.[21 22] Since patients with HSD often display strength impairments in the shoulder and decreased musculoskeletal tissue stiffness,[23 24] it is anticipated that they may benefit from the effects of high-load strengthening to improve active joint stability.

Many clinicians use low-load strengthening exercise, hesitating to use high-load strengthening exercise for patients with HSD due to uncertainty about patient safety and treatment effectiveness and because current guidelines recommend against high-load strengthening.[25] Our recent feasibility study on HSD and shoulder symptoms showed that patients could tolerate a 16-week high-load shoulder strengthening programme, with clinical benefits in self-reported shoulder function and objective clinical measures.[26]

The current randomised controlled trial (RCT) aimed to compare the short-term effectiveness of high-load versus low-load shoulder strengthening exercise on self-reported function in patients with HSD and persistent shoulder symptoms. Our primary hypothesis was that high-load shoulder strengthening exercise was superior to low-load exercise (standard care).

METHODS

Design and setting

We conducted a two-group, multicentre, superiority RCT where patients with HSD and shoulder symptoms were recruited from primary care within the Region of Southern Denmark, representing a general patient population in Denmark, between March 2019 and September 2020, with the primary endpoint being postintervention at 16-week follow-up. A total of 23 physiotherapists were chosen to deliver both interventions after receiving a 3-hour training programme. We ensured fidelity by controlling exercise logs, controlling patient payments from the university office to the clinics (no patients received more than the planned sessions: up to 32 for the intervention group and 3 for the comparator), and we controlled how many dumbbells we gave to the clinics. The trial was prospectively registered on ClinicalTrials.gov, and the trial protocol has previously been published elsewhere.[27]

A project manager was responsible for randomisation procedures and practical management of the project. Outcome assessments were completed at two sites by one of four blinded physiotherapists trained in study procedures but not otherwise involved in the project.

Participants

Patients were eligible for inclusion if aged 18–65 and fulfilling the generalised HSD (G-HSD) or historical HSD (H-HSD) criteria.[8 28] The criteria for HSD included musculoskeletal manifestations (ie, chronic shoulder pain and/or shoulder instability symptoms for at least 3 months without any cut-off for symptom intensity[27]) and the presence of generalised joint hypermobility (GJH), which was established using the Beighton score (cut-point of 4 for men of all ages and women ≥50 years and 5 for women <50 years).[28] For H-HSD, a 1-point lower Beighton score was accepted if the patient had a positive 5-part Questionnaire (5PQ) (cut-point of 2).[29] No shoulder laxity/instability tests were used as inclusion criteria to avoid false negative results due to patients' other symptoms.

The exclusion criteria were clinically suspected referred pain from the cervical spine decided by the referring general practitioner; diagnosis of systemic inflammatory rheumatic diseases, connective tissue diseases (except hypermobile Ehlers-Danlos Syndrome) and/or neurological diseases; pregnancy or childbirth within the past year or planning to get pregnant during the trial period (due to increased levels of relaxin); shoulder surgery within the last year or inability to speak or understand Danish, comply with the trial protocol or provide informed consent. After trial commencement, we added to the exclusion criteria steroid injection in the affected shoulder within 3 months to ascertain that the injection effect had diminished. However, no patients recruited prior to this change had received steroid injections within 3 months.

All patients answered an online pre-screening questionnaire at the initial eligibility assessment, including the 5PQ[29] and questions about shoulder symptoms via REDCap. The first author physically screened potentially eligible patients with shoulder symptoms using the Beighton tests[28 30] to classify GJH and later diagnose the patients with HSD. If eligible, patients consenting to participate were baseline tested and subsequently randomised. They were offered their first intervention session, preferably within 1 week after baseline testing or as close to that as practically possible. Patients were told that the trial compared two different exercise protocols to increase shoulder muscle function without revealing the direction of our hypothesis to control for expectation and performance bias.

Randomisation, allocation concealment and blinding

The allocation sequence was computer-generated with balanced block randomisation (block size 4–6), set up by an external data manager. Immediately following the baseline testing, the project manager completed the randomisation automatically in REDCap. To ensure allocation concealment, everyone was blinded to block sizes and unaware of the following assignment in the allocation sequence. The first author and outcome assessors were kept blinded from group allocation. The physiotherapists responsible for delivering interventions were not blinded to which treatment the patients had been allocated. A biostatistician (EB) performed the intention-to-treat (ITT) analyses of the primary outcome blinded to group allocation, and the remaining analyses were performed blinded by the first author.

Intervention

Both interventions have been described in detail in the published trial protocol following recommended guidelines.[27 31–33] The interventions were delivered at a physiotherapy clinic near the patients' homes, and the project covered all patient treatment expenses. All patients received education in scapular correction and joint protection adapted from the Danish Rheumatism Association.[34] Acceptable symptoms (<5/10 on a numerical pain rating scale) were allowed.[35] Patients filled out a printed exercise logbook with information about pain intensities, load,

progressions, repetitions, sets and adverse events at each session. Patients were encouraged to limit concomitant treatment (ie, manual therapy and steroid injection), of the shoulder and if necessary, to receive only as few treatments as possible and report it on the weekly questionnaires.

High-load shoulder strengthening exercise (HEAVY, intervention)

All patients randomised to HEAVY were individually supervised twice a week and encouraged to self-train once a week at home. We used five exercises for scapular and rotator cuff muscles[18 3619]using custom-made adjustable 3D-printed dumbbells (0–1000 g) and regular dumbbells (2–15 kg): Side-lying external rotation in neutral, prone horizontal abduction, prone external rotation at 90° shoulder abduction, supine scapular protraction and seated scaption. The warm-up consisted of 5 min of unloaded exercises. At the first session, the physiotherapist conducted a 5-repetition maximum (RM) test to estimate 10 RM (Brzycki's formula[37]); high-load was individually adjusted to a similar relative load for every patient and did not necessarily mean the application of a high external load in kg. The first three weeks consisted of familiarisation (3 sets of 10, week 1 at 50% of 10 RM, week 2 at 70% of 10 RM, week 3 at 90% of 10 RM). The following six weeks (weeks 4–9) included 3 sets of 10 RM. From weeks 10 to 15, the training included 4 sets of 8 RM.[38 39] A tapering period was applied in week 16 to allow for the anabolic response before follow-up testing.

Standard care (LIGHT, comparator)

The LIGHT programme was designed to mimic standard care in Denmark, primarily consisting of self-training exercises performed three times weekly. Patients received an individual introduction to exercises and supervision at weeks 5 and 11, where new exercises were introduced. The programme included nine shoulder exercises[18–20]: phase 1 (isometric), posture correction; phase 2 (isometric), shoulder abduction, shoulder internal and external rotation with 90° flexion at the elbow joint against a wall, and standing weight-bearing in the shoulders against a table; and phase 3 (dynamic with a yellow Theraband), shoulder abduction, shoulder internal and external rotation at 90° flexion at the elbow joint and four-point kneeling with single-arm raising.

Outcomes

Primary outcome measure

The primary outcome was self-reported shoulder function measured using the Western Ontario Shoulder Instability Index (WOSI) developed for patients with shoulder instability.[40] The questionnaire has 21 questions, each marked on a 0–100 scale (0=no shoulder limitations), range of 0–2100 points.[40] The WOSI subdomains are physical symptoms (10 questions), sports/recreation/work (four questions), lifestyle (four questions) and emotion (three questions), and the questionnaire is responsive, valid, sensitive to change, and has a high test–retest reliability.[41] The minimal important change was previously defined as 10.4%[40] and 14%,[42] corresponding to 218.4 and 294 points on the WOSI total score. A Danish-validated digital version was used.[43]

Secondary outcome measures

Secondary self-reported outcome measures were: the WOSI subdomains; shoulder pain worst, least and the average for the past week (scale 0–10)[44]; discomfort due to shoulder symptoms other than pain (instability, subluxation, laxity) (scale 0–10)[45]; Patient-Specific Functional Scale (scale 0–10)[46]; Checklist Individual Strength, the subscale of fatigue (scale 8–56)[47]; the COOP/WONCA questionnaire (scale 6–30)[48 49]; Tampa Scale of Kinesiophobia-11 (scale 11–44)[50]; European Quality of life-5 Dimensions-5-Level Scale (scale <0–1)[51 52]; EQ-Visual Analogue Scale (scale 0–100)[52 53]; Global Perceived Effect (GPE) on each of the WOSI subdomains (7-point scales, range: 'worse, an important worsening' to 'better, an important improvement').[54 55]

Secondary objective outcome measures were: isometric shoulder torque strength (Nm/kg) in scaption, internal rotation and external rotation using a handheld dynamometer (IsoForce Dynamometer EVO2; Medical Device Solution AG)[56 57]; Active and passive shoulder range of motion in internal and external rotation in 90° shoulder abduction[56 58] and proprioception in low-range and midrange shoulder flexion angles[59 60] assessed using a digital goniometer (Halo, Halo Medical Devices, Subiaco, Australia); shoulder laxity, hypermobility and instability assessed using the anterior and posterior load and shift[61] (positive: 2 or 3, glenoid head farther than the glenoid), sulcus sign[61] (positive <1 cm), Gagey[61] (positive >105°), apprehension[61] (positive: pain/apprehension), relocation[61] (positive: reduction of pain/apprehension), release[61] (positive: reappearing of pain/apprehension), Rotés Qúerol[30] (positive >90°) and shoulder rotation (positive: total passive range of motion above 180°) and flexion (positive: the whole humerus rested on table) tests.[62]

Furthermore, patients were asked about their use of painkillers, concomitant treatment and adverse events. We did not make any changes to the outcomes after the trial commenced. The GPE was measured at postintervention only, adverse events were measured throughout the intervention period and the remaining outcome measures were assessed at baseline and postintervention.

Sample size

We powered the trial to detect a between-group difference of at least 252 points (12%) based on previously reported minimal important change in the absence of patient-derived minimal important difference (MID) on the WOSI total score,[40 42] with a 350 points SD (based on group differences from previous RCTs).[18 26] With a two-sided significance level of 0.05% and 90% power, a sample size of 42 per group was required to detect a statistically significant difference. We decided to enrol 50 patients per group (expected dropout rate 16%).[18 20]

Statistical methods

A statistical analysis plan (https://osf.io/afgn2/) and blinded interpretation (https://osf.io/muztx/) were publicly available before any analysis commenced. The baseline characteristics were presented using descriptive analyses as mean (SD), median (IQR) or proportion (n (%)). Continuous data were checked for normality using the Shapiro-Wilk test and visual inspection of histogram and quantile–quantile plot. The ITT analyses included all randomised patients. We used a multivariable linear regression model to assess the between-group difference at 16 weeks with the primary outcome (WOSI total) as the dependent variable, and treatment group as the main effect, after adjusting for WOSI baseline score, age, sex and clustering around clinic (using cluster-robust standard errors). For continuous secondary outcomes, similar models were used. Multivariable logistic regressions were used for binary outcomes to estimate between-group odds ratio (OR) postintervention, with outcomes (clinical shoulder tests and GPE) as dependent variables and treatment

group as the main effect, adjusted with the baseline score of the outcomes of interest and the same other variables. The assumptions underlying the regression models, including normality, homogeneity of variance of residuals and linearity for quantitative predictors were met. Since the secondary outcomes were supportive, we did not adjust for multiple testing. For adverse events, self-reported pain medication use and other concomitant treatments received, the crude difference between risks and medians were calculated with 95% confidence interval (CI) based on the 'as observed' data while still respecting the original group allocation. For adverse events, the adjusted (age, sex, clustering around clinic) risk difference was estimated using margins after fitting a logistic regression model. Multiple imputation was used for missing data at follow-up for withdrawals with age, sex, group allocation (masked) and WOSI baseline values as predictors. For sensitivity purposes, we used baseline values carried forward.

Per-protocol analyses were applied using the same methods. The per-protocol population for both groups was defined as those attending at least two-thirds (67%) of the 48 planned exercise sessions, completing the intervention, and not receiving steroid injections or surgery. We performed a post hoc analysis of the number of successful (above 252 points) patients in HEAVY/LIGHT and calculated the numbers needed to treat (NNT) as the inverse of risk differences, adjusted for sex, age and clustering around clinic (fitting generalised linear models for the binomial family). An alpha level of 0.05 (two-sided) was considered statistically significant. Stata V.16 was used for the statistical analyses.

Public and patient involvement

Patients (n=12) from our feasibility study were involved in the trial design by providing feedback on the outcome measures and exercise programme, as described previously.[26] No members of the public or patients were involved in the conduct or interpretation of this trial.

Deviations from the registered trial protocol

We made no deviations from our published protocol.[27]

RESULTS

Recruitment ran from March 2019, and the final 16-week follow-ups were completed in February 2021. Figure 1 shows the flow of patients through the trial. Of the 100 randomly assigned patients with HSD (none with hypermobile Ehlers-Danlos Syndrome), 93 patients (93%) were followed up postintervention.

Patients were mainly women (79%), had a mean age of 37.8 years, with a mean Beighton score of 5.8 (table 1, online supplemental file 1). A total of 67 patients (HEAVY 34, LIGHT 33)

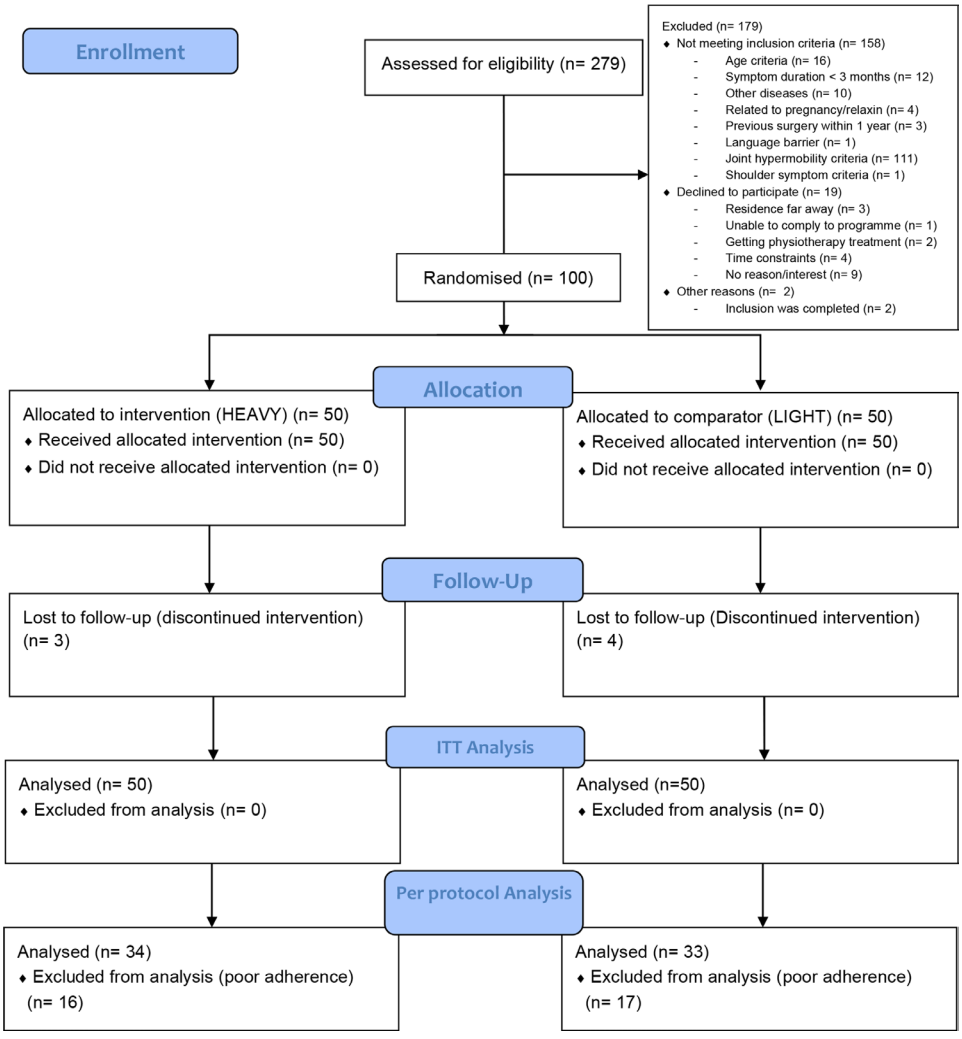

Figure 1 CONSORT flow diagram. ITT, intention-to-treat.

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Table 1 Baseline characteristics for the intervention (HEAVY) and comparator (LIGHT) in patients with hypermobility spectrum disorder and shoulder symptoms

Variables	LIGHT, n=50	HEAVY, n=50
Sex (female), n (%)	39 (78)	40 (80)
Age (years)	37.0 (12.0)	38.6 (13.6)
Weight (kg)	81.6 (16.0)	79.0 (18.5)
Height (cm)	172.4 (9.2)	171.4 (8.9)
Hypermobility spectrum disorder		
Beighton score (scale 0–9)	5.8 (1.8)	5.8 (1.6)
5PQ (scale 0–5)	3.1 (1.2)	2.9 (1.1)
Generalised HSD, n (%)	40 (80)	47 (94)
Historical HSD, n (%)	10 (20)	3 (6)
Dominant writing hand (right), n (%)	48 (96)	43 (86)
Symptomatic shoulder (right), n (%)	30 (60)	27 (54)
Symptom duration (median months)	36 (11.8, 87)	43 (14.3, 120)
Previous shoulder dislocation (yes), n (%)	8 (16)	10 (20)
Feeling shoulder is loose (yes), n (%)	26 (52)	22 (44)
Primary outcome measure		
WOSI total (scale 0–2100)	1071.5 (379.8)	1042.1 (351.9)

Continuous data are presented as mean (SD) or median (IQR), and categorical variables are presented as proportion n (%).
HSD, hypermobility spectrum disorder; 5PQ, 5-part Questionnaire; WOSI, Western Ontario Shoulder Instability Index.

adhered to the interventions and constituted the per-protocol population. The reason for non-adherence was completing less than 32 exercise sessions (n=33); two patients from LIGHT had received steroid injections during the intervention.

Primary outcome

In the ITT analysis, HEAVY led to a greater improvement in shoulder function than LIGHT postintervention (WOSI total, adjusted mean difference, −174.5; 95% CI −341.4 to −7.7, 8.3%) (table 2). The adjusted mean difference was below the predefined MID. The per-protocol analysis demonstrated an even larger benefit favouring HEAVY (WOSI total, adjusted mean difference −250.7; 95% CI −323.4 to −178.0, 12%). The sensitivity analyses supported these findings (online supplemental file 3). The proportion of patients with a clinically relevant outcome favoured HEAVY (ITT 68% vs 54%), NNT 7 (95% CI 4 to 620), adjusted for age, sex and clustering around clinic; per-protocol 85% versus 55%, NNT 3 (95% CI 2 to 7), adjusted for age, sex and clustering around clinic.

Secondary outcomes

The secondary outcomes favoured HEAVY, but most were non-significant and with large CIs (table 2, online supplemental files 3 and 4). Postintervention, patients in HEAVY were less likely to have a positive shoulder rotation test (OR 0.32, 95% CI 0.13 to 0.80), and higher odds of rating an important improvement for 'physical symptoms' in GPE (OR 2.37, 95% CI 1.07 to 5.24). There were no serious adverse events, and HEAVY was associated with significantly more transient muscle soreness and headaches (table 3, per-protocol in online supplemental file 5). Two patients from HEAVY dropped out due to adverse events (table 3). There were no differences between the use of painkillers and concomitant treatment between the groups at baseline and post-intervention (online supplemental file 2).

DISCUSSION

HEAVY led to an 8.3% greater improvement in self-reported shoulder function than LIGHT at 16-week follow-up. Most secondary outcomes were inconclusive due to large CIs, but patients in HEAVY were less likely to have a positive shoulder rotation >180° and more likely to rate an important improvement in 'physical symptoms'. There were no serious adverse events, but more patients undergoing HEAVY experienced transient muscle soreness and headaches.

Our findings align with the between-group difference in WOSI (11.1% at 12 weeks) in a trial on multidirectional instability favouring a strengthening programme progressing in load and functional range of motion compared with strengthening primarily in 0 degrees of elevation.[18] Furthermore, our results support that exercise is a relevant and important treatment option for shoulder conditions.[63 64]

A priori, we defined the MID as a between-group difference of at least 12% (252 points). The mean between-group difference postintervention (8.3%, 174.5 WOSI total score) was statistically significant but below the MID, while the per-protocol analysis reached the MID (11.9%). When interpreting the results, it is important to acknowledge that the available MID thresholds are based on within-group changes, while the MID should be applied to changes in the number of individual patients, and not only group changes.[65 66] Although the post hoc analysis supported that 14% more patients in HEAVY reached improvements above 12%, at least 20% of additional improvements on pain and disability have been suggested as the cut point to consider that the effect of physiotherapy is worthwhile.[67] Therefore, the clinical relevance of the between-group difference remains unclear.[68] However, our finding adds to the debate regarding the relevance of prescribing additional doses of shoulder strengthening as a treatment for shoulder conditions, suggesting that progressive high-load strengthening may be relevant for the current population with HSD and shoulder symptoms.[69 70]

The rationale for using HEAVY was to impact the muscle cross-sectional areas and the voluntary activation of the available muscle mass to pose active joint stability to compensate for the lack of passive stability in hypermobile shoulders.[27] However, the mechanisms behind the effect of HEAVY are complex and also include psychosocial aspects and contextual effects.[71] Our findings, although non-significant, regarding the between-group difference in muscle strength in favour of HEAVY (scaption 10.4%, external rotation 12%) and the trend in less positive clinical tests (an indirect measure of muscle-tendon stiffness) may explain some of the effect of HEAVY on self-reported shoulder function and decreased physical symptoms. However, considering that several studies on shoulder pain-related conditions have failed to show superiority of progressive high-load strengthening exercise could indicate that other factors than the physical response to load are important.[19 69 70] Other factors may include the different types of exercise used in HEAVY and LIGHT (eg, full range or not) and the benefits of supervised and individually graded exercise to restore the ability of daily activities. This may have resulted in higher confidence and self-efficacy related to better function and psychosocial measures, such as shoulder related mental well-being and quality of life, which are components covered in WOSI total.[72 73]

HEAVY led to more transient muscle soreness and headache, considered minor and acceptable adverse events.[74] Muscle soreness can be seen as an important response to high-load strengthening exercise that should not be a barrier to successful treatment outcomes.[75] Besides patient education and intensive

Table 2 Outcomes at 16-week follow-up for the intervention (HEAVY) and comparator (LIGHT) in patients with hypermobility spectrum disorder and shoulder complaints

	Total no. of assessments (LIGHT/HEAVY)*	Mean at 16 weeks in LIGHT (95% CI) n=50	Mean at 16 weeks in HEAVY (95% CI) n=50	Between-group difference at 16 weeks (crude) (95% CI)	Between-group difference at 16 weeks (adjusted)† (95% CI)
Primary outcome measure					
WOSI total (scale 0–2100)	96/97	802.6 (683.9 to 921.3)	606.9 (481.1 to 732.7)	**−195.7 (−367.7 to -23.7)**	**−174.5 (−341.4 to -7.7)**
Secondary self-reported outcomes					
WOSI physical symptoms (scale 0–1000)	96/97	346.5 (286.9 to 406.2)	279.0 (222.4 to 335.6)	−67.5 (−149.3 to 14.3)	−68.6 (−144.7 to 7.4)
WOSI sports/recreation/work (scale 0–400)	96/97	150.7 (121.6 to 179.9)	111.8 (82.4 to 141.2)	−38.9 (−79.4 to 1.6)	−30.7 (−70.6 to 9.2)
WOSI lifestyle (scale 0–400)	96/97	134.5 (108.3 to 160.8)	96.6 (70.1 to 123.0)	**−38.0 (−74.8 to -1.1)**	−31.2 (−63.1 to 0.8)
WOSI emotions (scale 0–300)	96/97	169.3 (147.9 to 190.8)	121.7 (98.8 to 144.6)	**−47.6 (−78.9 to -16.4)**	**−43.5 (−72.0 to -14.9)**
Shoulder pain last 7 days (scale 0–10)					
Lowest rating	95/97	1.3 (0.7 to 1.9)	1.1 (0.6 to 1.6)	−0.2 (−1.0 to 0.5)	−0.3 (−1.0 to 0.4)
Highest rating	95/97	4.0 (3.2 to 4.8)	2.8 (2.1 to 3.5)	**−1.2 (−2.2 to -0.1)**	−1.0 (−2.0 to 0.1)
Average rating	95/97	2.3 (1.6 to 2.9)	1.7 (1.1 to 2.3)	−0.6 (−1.4 to 0.3)	−0.5 (−1.5 to 0.5)
Discomfort due to shoulder symptoms other than pain last 7 days (scale 0–10)					
Lowest rating	95/97	1.3 (0.8 to 1.7)	1.1 (0.6 to 1.6)	−0.1 (−0.8 to 0.5)	−0.2 (−0.9 to 0.5)
Highest rating	95/97	3.0 (2.3 to 3.7)	2.2 (1.6 to 2.8)	−0.8 (−1.7 to 0.1)	−0.6 (−1.2 to 0.1)
Average rating	95/97	1.9 (1.4 to 2.5)	1.5 (1.0 to 2.1)	−0.4 (−1.1 to 0.3)	−0.2 (−0.9 to 0.4)
Patient-Specific Functional Scale (scale 0–10)	95/97	5.6 (4.8 to 6.3)	5.7 (5.0 to 6.5)	0.2 (−0.9 to 1.3)	0.2 (−1.0 to 1.4)
Checklist Individual Strength (scale 8–56)	95/97	32.5 (28.7 to 36.3)	29.8 (26.4 to 33.1)	−2.7 (−7.7 to 2.3)	−2.5 (−7.1 to 2.2)
COOP/WONCA (scale 6–30)	94/97	14.0 (12.7 to 15.3)	12.9 (11.6 to 14.1)	−1.2 (−3.0 to 0.6)	−0.5 (−2.2 to 1.2)
Tampa Scale of Kinesiophobia (scale 11–44)	94/97	22.2 (20.4 to 24.1)	20.5 (18.8 to 22.1)	−1.8 (−4.2 to 0.7)	−0.8 (−2.7 to 1.1)
EQ-5D-5L (scale <0–1)	94/97	0.76 (0.72 to 0.79)	0.80 (0.76 to 0.83)	0.04 (−0.01 to 0.09)	0.02 (−0.02 to 0.07)
EQ-VAS (scale 0–100)	94/97	69.6 (64.0 to 75.2)	75.3 (70.6 to 80.1)	5.7 (−1.5 to 13.0)	0.3 (−8.0 to 8.6)
Secondary objective outcomes					
Range of motion (°)					
Internal rotation passive	87/90	72.6 (67.3 to 78.0)	69.9 (64.7 to 75.2)	−2.70 (−10.6 to 5.2)	−0.6 (−11.3 to 10.2)
Internal rotation active	87/90	68.9 (64.1 to 73.7)	71.2 (66.8 to 75.7)	2.4 (−4.5 to 9.2)	4.0 (−4.2 to 12.2)
External rotation passive	87/90	105.3 (96.9 to 113.7)	107.6 (100.0 to 115.1)	2.2 (−9.8 to 14.3)	−0.5 (−16.4 to 15.4)
External rotation active	87/90	100.6 (93.2 to 108.1)	107.0 (100.5 to 113.6)	6.4 (−4.2 to 17.0)	3.4 (−10.8 to 17.5)
Isometric shoulder torque strength (Nm/kg)					
Scaption	87/90	0.48 (0.42 to 0.54)	0.52 (0.45 to 0.59)	0.04 (−0.05 to 0.14)	0.05 (−0.04 to 0.13)
Internal rotation	87/90	0.37 (0.32 to 0.42)	0.36 (0.30 to 0.41)	−0.01 (−0.09 to 0.06)	0.00 (−0.07 to 0.07)
External rotation	87/90	0.25 (0.22 to 0.28)	0.27 (.23 to 0.31)	0.02 (−0.03 to 0.07)	0.03 (−0.03 to 0.08)
Proprioception in flexion (error °)					
Low range	87/90	4.65 (3.71 to 5.60)	4.98 (3.85 to 6.11)	0.33 (−1.24 to 1.90)	0.65 (−1.60 to 2.90)
Mid-range	86/90	3.34 (2.65 to 4.04)	4.51 (3.47 to 5.54)	**1.17 (0.01 to 2.32)**	1.17 (−0.27. 2.60)
Shoulder instability and laxity tests (positive %)‡					
Shoulder flexion test, positive=yes	87/90	78 (64 to 91)	62 (47 to 76)	OR 0.46 (0.17 to 1.21)	OR 0.40 (0.09 to 1.75)
Shoulder rotation test, positive >180°	87/90	62 (47 to 76)	42 (28 to 56)	OR 0.44 (0.19 to 1.03)	**OR 0.32 (0.13 to 0.80)**
Apprehension test, positive=yes	87/90	70 (55 to 85)	62 (48 to 76)	OR 0.70 (0.29 to 1.65)	OR 0.59 (0.31 to 1.13)
Relocation test,§ positive=yes	87/90	55 (38 to 72)	44 (30 to 58)	OR 0.66 (0.28 to 1.56)	OR 0.59 (0.33 to 1.08)
Release test,§ positive=yes	87/90	50 (32 to 68)	37 (23 to 51)	OR 0.58 (0.24 to 1.39)	OR 0.58 (0.25 to 1.35)
Load and shift anterior, positive 2–3	87/90	68 (52 to 84)	62 (47 to 77)	OR 0.77 (0.31 to 1.90)	OR 0.56 (0.23 to 1.40)
Load and shift posterior, positive 2–3	87/90	28 (13 to 44)	18 (7 to 29)	OR 0.57 (0.20 to 1.61)	OR 0.63 (0.19 to 2.04)
Sulcus sign, positive >1 cm	87/90	84 (68 to 93)	85 (70 to 93)	OR 0.97 (0.28 to 3.34)	OR 1.05 (0.28 to 3.94)
Gagey, positive >105°	87/90	92 (85 to 100)	90 (78 to 100)	OR 0.73 (0.15 to 3.43)	OR 0.43 (0.14 to 1.37)
Rotés Queról, positive >90°	87/90	63 (48 to 77)	55 (41 to 69)	OR 0.73 (0.31 to 1.72)	OR 0.72 (0.20 to 2.66)
Global Perceived Effect‡¶					
(% rated important effect postintervention)					
Physical symptoms	45/47	44 (31 to 59)	64 (49 to 76)	OR 2.21 (0.96 to 5.09)	**OR 2.37 (1.07 to 5.24)**
Sports/recreation/work	45/47	38 (25 to 53)	51 (37 to 65)	OR 1.72 (0.75 to 3.94)	OR 1.82 (0.82 to 4.03)
Lifestyle	45/47	44 (31 to 59)	55 (41 to 69)	OR 1.55 (0.68 to 3.52)	OR 1.60 (0.65 to 3.96)
Emotions	45/47	40 (27 to 55)	51 (37 to 65)	OR 1.57 (0.69 to 3.58)	OR 1.57 (0.51 to 4.85)

Statistically significant results (p<0.05) are marked with bold.
*There were 100 possible assessments for each group (50 at baseline and 50 at 16 weeks follow-up), except for Global Perceived Effect which had 50 possible assessments for each group.
†The results are adjusted for baseline score, age, sex and the clustering around physiotherapy clinic.
‡Proportions of positive test in % (95% CI) and OR for between-group differences with group LIGHT as reference.
§Relocation and release tests were only performed on patients with a positive apprehension test.
¶No data imputation.
COOP/WONCA, Dartmouth Primary Care Cooperative Research Network/World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians; EQ-5D-5L, European Quality of life-5 Dimensions-5-Level; VAS, visual analogue scale; WOSI, Western Ontario Shoulder Instability Index.

Table 3 Adverse events (specific, serious or minor, and withdrawals due to adverse events), and crude difference between risks and medians were calculated with 95% CIs based on the 'as observed' data while still respecting the original group allocation, from baseline to 16-week follow-up for the intervention (HEAVY) versus comparator (LIGHT) in patients with hypermobility spectrum disorder and shoulder symptoms

Adverse events	LIGHT (n=46)	HEAVY (n=45)	Between-group risk difference or median difference with 95% CI (crude)*
Number of patients reporting serious adverse events†	0 (0)	0 (0)	0 (0 to 0)
Number of patients reporting minor adverse events (n (%))	24 (52)	29 (64)	12 (–8 to 32)
Index shoulder			
Muscle soreness	17 (37)	25 (56)	19 (–2 to 39)
Shoulder is locked	3 (4)	2 (4)	–2 (–11 to 7)
Subluxation	3 (7)	1 (2)	–4 (–12 to 4)
Dislocation	0 (0)	1 (2)	2 (–2 to 7)
Persistent worsening of symptoms	8 (17)	8 (18)	0 (–15 to 16)
Other sites than index shoulder			
Headache	9 (20)	18 (40)	**20 (2 to 39)**
'Other' minor events related to index shoulder or other sites	18 (39)	19 (42)	3 (–17 to 23)
Total number of adverse events			
Number of minor adverse events (median (95% CI)‡	1 (0 to 1.1)	2 (0.4 to 4.0)	1 (–0.6 to 2.6)
Index shoulder			
Muscle soreness	0 (0 to 1)	1 (0 to 2)	1 (–0.1 to 2.1)
Shoulder is locked	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Subluxation	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Dislocation	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Persistent worsening of symptoms	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)
Other sites than index shoulder			
Headache	0 (0 to 0)	0 (0 to 1)	0 (0 to 0)
'Other' minor events related to index shoulder or other sites	0 (0 to 1)	0 (0 to 1)	0 (0 to 0)
Number of dropouts due to adverse events (n, (%))	0 (0)	2 (4)§	4 (–2 to 10)

This table includes all adverse events that occurred during the 16-week study period, but which did not necessarily have a causal relationship with the treatment administered. Statistically significant results (p<0.05) are marked with bold.
*The adjusted (age, sex, clustering around clinic) risk difference using margins after fitting a logistic regression model did not change the estimates (online supplemental file 6).
†Serious adverse events were unexpected but covered death, life-threatening events, disability and permanent damage.
‡For each patient, each adverse event could count 0–16 times corresponding with 16 weeks intervention period.
§One dropout due to worsening of symptoms caused by lack of supervision during COVID-19 pandemic, and one patient had suffered from a hand fracture not related to the intervention (data not included in table 3).

supervision to manage potential symptom flares, the current trial did not employ manual therapy or other physiotherapy modalities to gain short-term relief (eg, from headaches) that could have increased exercise adherence.[64 76]

This trial has limitations. We developed LIGHT as an active comparator to mimic the average exercise-based standard treatment offered across physiotherapy clinics in Danish primary care. Since there is a considerable variation in treatments among clinicians, we could potentially have offered the patients a better or worse treatment than they would have received usually. However, LIGHT is considered a better approach than wait-and-see or no treatment for this patient group.[63 77] We were unable to blind patients, and the nature of the intervention meant that we could not blind the treatment providers, but we presented both interventions as having the potential to be effective. It is, however, possible that the treating physiotherapists could have favoured one intervention over the other (care provider bias). The two interventions in this trial are of varying complexity in training and delivery, with the number of supervised sessions being one of the major differences between interventions. Because HEAVY is a new exercise approach, it was deemed important to provide intensive supervision to manage potential adverse events and adequate load progression. Although there is convincing evidence that supervised exercise and self-training are equally effective for shoulder conditions, thereby decreasing the risk of attention bias,[63] it is unknown whether this can be extended to patients with HSD as they may have decreased tissue stiffness and difficulties in performing strengthening exercise unsupervised, which may compromise patient safety. Furthermore, the generalisability to patients with hypermobile Ehlers-Danlos Syndrome, patients referred to secondary care (eg, specialised hypermobility units), and other international/cultural settings is unanswered. Many of the CIs were inconclusive, reflecting low precision of the trial estimates. We did not adjust for multiple testing since all secondary outcomes were declared supportive. However, we cannot rule out statistical significance by chance for the secondary outcomes. Furthermore, the validity of the trial results depends on the correct specification of the regression models as well as imputation model. The issue of unmeasured random confounding (and adjustment for few confounders) may be considered as a limitation of the trial. The measurement bias in the ITT estimates is a limitation but the WOSI baseline score for those patients who were and were not in the per-protocol population did not differ. Although relevant, it was not within the scope of this trial to evaluate the cost-effectiveness of the interventions. Still, it may be conducted later using the Danish national registries.

This trial had strengths. The pragmatic approach of this trial using broad eligibility criteria, a consecutive sampling strategy, standard care as the comparator, and patients recruited from primary care improve the generalisability of the findings. The pre-registration at ClinicalTrials.gov and publication of the a

priori trial protocol, statistical analysis plan, blinded interpretation of the findings, and thoroughly described exercise protocols based on established frameworks greatly improve the overall quality of the current study and the potential for implementation.

In conclusion, supervised, progressive, high-load strengthening exercise was statistically superior to less supervised and less progressive, low-load exercise and may be used as treatment in patients with HSD and shoulder symptoms in primary care to improve shoulder function. However, only eight percent of the secondary outcomes significantly supported the primary outcome. Clinicians should pay attention to and help alleviate minor transient symptoms following the treatment. Further studies are needed to confirm the clinical relevance, the long-term effectiveness and the underlying mechanisms of high-load strenghtening exercise.

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Contributors BL and BJ-K conceived the study idea. All authors initiated the study design. BL, BJ-K, STS and JS helped with the implementation. BL, BJ-K and EB provided statistical expertise in the study design and planning of the primary and secondary statistical analyses. EB performed the blinded intention-to-treat analysis of the primary outcome. BL, BJ-K, STS and KS contributed to the design of the study intervention. BL was the grant holder and principal investigator and responsible for patient inclusion and data collection. BL trained the study personnel in testing procedures. BL drafted this paper, and all authors have been involved in drafting versions and critically revising it for important intellectual content and have read and approved the final version. BL is the guarantor of the study.

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