Progressive high load strength training in patients with hypermobility spectrum disorders and shoulder complaints

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PROGRESSIVE HIGH LOAD STRENGTH TRAINING IN PATIENTS WITH HYPERMOBILITY SPECTRUM DISORDERS AND SHOULDER COMPLAINTS

PhD Thesis

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Preface

The work presented in this thesis was carried out during my employment as a PhD fellow at the University of Southern Denmark (2018-2022), under the main supervision of Dr Birgit Juul-Kristensen, focusing on progressive high load strength training in patients with joint hypermobility and shoulder complaints.

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Finally, in particular regard to my nearest family – only your presence, love, and support make my professional life meaningful.

Behnam Liaghat, Odense, Denmark.

Absorb what is useful
Discard what is not
Add what is uniquely your own.
(Lee Jun-fan/Bruce Lee)

Publications included in the PhD thesis

The thesis is based on the following papers:

I. **Feasibility study**
Liaghat B, Skou ST, Jørgensen U, Sondergaard J, Søgaard K, Juul-Kristensen B. *Heavy shoulder strengthening exercise in people with hypermobility spectrum disorder (HSD) and long-lasting shoulder symptoms: a feasibility study*. Pilot Feasibility Stud. 2020 Jul 10; 6:97. doi: 10.1186/s40814-020-00632-y.

II. **Protocol for a randomised controlled trial**
Liaghat B, Skou ST, Søndergaard J, Boyle E, Søgaard K, Juul-Kristensen B. *A randomised controlled trial of heavy shoulder strengthening exercise in patients with hypermobility spectrum disorder or hypermobile Ehlers-Danlos syndrome and long-lasting shoulder complaints: study protocol for the Shoulder-MOBILEX study.* Trials. 2020 Dec 1;21(1):992. doi: 10.1186/s13063-020-04892-0.

III. **Baseline clinical characteristics**
Liaghat B, Skou ST, Sondergaard J, Boyle E, Søgaard K, Juul-Kristensen B. *Clinical characteristics of 100 patients with hypermobility spectrum disorders and shoulder discomfort with or without mechanical symptoms: A cross-sectional study.* Arch Phys Med Rehabil. 2022 Jan 20:S0003-9993(22)00017-X. Epub ahead of print.

IV. **Randomised controlled trial primary endpoint**
Liaghat B, Skou ST, Sondergaard J, Boyle E, Søgaard K, Juul-Kristensen B. *Short-term effectiveness of high-load strengthening exercise in patients with hypermobile shoulders: A randomised controlled trial*. In review (second revision) for publication in BJSM. 2022 Feb.

Contents

Thesis at a glance

Paper	I Feasibility study	II Protocol	III Clinical characteristics	IV Randomised controlled trial
Objective	To evaluate the feasibility of a 16-week progressive high load shoulder strengthening exercise programme for improving shoulder function in people with hypermobility spectrum disorders (HSD) or hypermobile Ehlers-Danlos syndrome (hEDS) and persistent shoulder complaints.	To develop and describe a study protocol including progressive high load (HEAVY) and less progressive low load (LIGHT) shoulder strengthening exercise programmes targeting patients with HSD/HEDS and persistent shoulder complaints.	To describe the clinical characteristics of patients with HSD/HEDS and shoulder complaints with or without mechanical shoulder symptoms and compare variables that differed between the two subgroups.	To investigate the short-term effectiveness of a 16-week progressive high load shoulder strengthening exercise programme (HEAVY) vs LIGHT in patients with HSD/HEDS and persistent shoulder complaints seeking primary care.
Participants	Twelve patients (11 females, mean age 39.3) with HSD and shoulder instability and/or shoulder pain for at least three months.	Patients between 18-65 years with HSD/ hEDS and shoulder instability and/or shoulder pain for at least three months.	One hundred patients (79 females, mean age 37.83) with HSD and shoulder instability and/or shoulder pain for at least three months from primary care in Denmark.	
Methods	16-week progressive high load shoulder strength training three times weekly with exercises targeting scapular and rotator cuff muscles. Primary outcomes were predefined research progression criteria, including recruitment rate, assessment duration, patient retention, training adherence, and adverse events, besides patient and physiotherapist feedback. Secondary outcomes were self-reported and objectively measured outcomes.	A protocol for a high-quality superiority, parallel-group, RCT, comparing HEAVY and LIGHT (usual care), was developed, including considerations about improved recruitment methods, sample size, and statistical methods.	Medical history, self-reported and objective characteristics on shoulder pain, discomfort due to mechanical shoulder symptoms, shoulder function, fatigue, fear of movement, quality of life, and additional treatment were collected by external blinded physiotherapists. Mechanical shoulder symptoms were defined as self-reported shoulder instability, subluxation, and/or laxity (rated as Yes/No).	A superiority, parallel-group, randomised controlled trial. Patients were randomised to receive HEAVY (full range of motion, high load) or LIGHT (neutral to midrange of movement, low load) strengthening exercise programmes three times weekly with exercises targeting the scapular and rotator cuff muscles. The primary outcome was the between-group difference at 16-week follow-up in the Western Ontario Shoulder Instability Index (WOSI, 0-2100 better to worse) and a wide range of secondary outcomes related to pain, function, and quality of life.
Conclusion	The shoulder strengthening exercise programme was feasible and tolerable for patients with HSD and persistent shoulder complaints. All requirements for a future RCT were met, except for the recruitment rate that needed to be optimised.	A high-quality RCT, comparing HEAVY and LIGHT, was designed, described, published in an open-access journal, and initiated with an aimed inclusion of 100 patients.	All patients had substantial impairments related to shoulder pain, function, fatigue, fear of movement, and quality of life. Sixty-seven patients reported mechanical shoulder symptoms. They were younger and more severely impaired than those without mechanical shoulder symptoms. This highlights the importance of addressing mechanical shoulder symptoms during treatment to address the patients' impairments fully.	HEAVY was statistically superior to LIGHT and may be used as treatment in people with HSD and shoulder complaints in clinical practice to alleviate shoulder symptoms and improve shoulder function in the short term. Patients should be supported to manage minor adverse events (transient soreness and headaches). However, further studies are needed to confirm the clinical relevance of the between-group difference, explain the underlying mechanisms, and investigate the long-term effectiveness.

English summary

Introduction

Joint hypermobility is characterised by the ability to move the joints beyond the normal range of motion. Symptomatic joint hypermobility is now called hypermobility spectrum disorders (HSD). At least four out of five patients with HSD experience shoulder complaints, including persistent pain and mechanical shoulder symptoms (instability, subluxation, laxity). However, no studies have focused on exercise-based treatment for the shoulder in this patient group. Progressive high load strength training generally results in a marked increase in muscle cross-sectional area, neural drive, and increased tendon stiffness. These are essential components of acquiring active shoulder stability during movement tasks and daily life. Because patients with HSD often display decreased strength and increased shoulder laxity/instability, they may benefit from strengthening the shoulder muscles using progressive high load strengthening. However, many clinicians hesitate to use high load exercise in patients with HSD due to uncertainty about patient safety, treatment effectiveness and because current guidelines recommend against high load exercise for this population. As such, no studies have assessed the effect of a progressive, high load strengthening programme on patients with HSD.

Objectives

The overall objective was to investigate patients with HSD and persistent shoulder complaints and the effectiveness of progressive high load strength training as treatment. The specific study aims were:

I) to investigate the feasibility of using progressive high load strength training among patients with HSD and persistent shoulder complaints.

II) to develop and describe a study protocol including a progressive high load (HEAVY) and less progressive low load (LIGHT) shoulder strengthening exercise programmes, targeting patients with HSD.

III) to describe the shoulder impairments of patients with HSD, focusing on differences between patients with and without self-reported mechanical shoulder symptoms

IV) in a randomised controlled trial (RCT) to investigate the effectiveness of a 16-week HEAVY programme compared with LIGHT (usual care) in patients with HSD and persistent shoulder complaints seeking primary care. The main hypothesis was that HEAVY is superior to LIGHT in improving self-reported shoulder function.

Methods

I) Patients underwent a HEAVY programme three times weekly using exercises targeting scapular and rotator cuff muscles. Primary outcomes were predefined research progression criteria, including recruitment rate, assessment duration, patient retention, training adherence, and adverse events, besides patient and physiotherapist feedback. Data were treated with descriptive statistics and paired t-tests.

II) A protocol for a high-quality superiority, parallel-group, RCT comparing HEAVY and LIGHT (usual care) was designed and described, including considerations about improved recruitment methods, sample size, and statistical methods.

III) Baseline data from the RCT was used. Medical history, self-reported and objective characteristics on shoulder pain, shoulder discomfort due to mechanical shoulder symptoms, shoulder function, fatigue, fear of movement, shoulder related quality of life, and additional treatment were collected by external blinded physiotherapists. Mechanical shoulder symptoms were defined as self-reported shoulder instability, subluxation, and/or laxity (rated as Yes/No). Data were treated with descriptive statistics and logistic regression analyses.

IV) Patients were randomised to receive a HEAVY or LIGHT three times weekly with exercises targeting scapular and rotator cuff muscles. The primary outcome was the between-group difference at 16-week follow-up in the Western Ontario Shoulder Instability Index (WOSI, 0-2100 better to worse) and self-reported and objective secondary outcomes. Data were treated with multivariable linear regression, multivariable logistic regression, generalised linear model, and quantile regression.

Results

I) Twelve patients were included. The recruitment rate was 5.6/month, assessment duration (mean ± SD) 105 ± 9 min, retention 100%, adherence 83%, and four patients experienced short-lasting soreness or pain. Patient feedback was positive, and the physiotherapists found the intervention relevant and applicable to the patient group.

II) The HEAVY programme consisted of five shoulder exercises. A 5-repetition maximum (RM) test was conducted at the first session to estimate the 10 RM. The first three weeks consisted of a familiarisation period progressing from three sets of a load of 50% of 10 RM in week one, to 70% of 10 RM in the second week and to 90% of 10 RM in the third week. The following six weeks (weeks 4–9) included three sets of 10 RM, and from weeks 10–15, the training load was four sets of 8 RM. A tapering period was applied in week 16 to allow the anabolic response before follow-up testing. The LIGHT programme consisted of nine exercises. Phase 1 (weeks 1-4) consisted of isometric scapula setting; Phase 2 (weeks 5-10) included isometric shoulder exercises in a neutral position. In weeks 11-13, a combination of isometric and dynamic exercises midrange

using a TheraBand. In Phase 3 (weeks 14-16), the exercises were dynamic to midrange. Patients in HEAVY were supervised twice weekly, and patients in LIGHT received supervision three times during the 16-week intervention.

III) Sixty-seven of 100 patients reported mechanical shoulder symptoms. Patients in both groups said impairments related to shoulder pain, shoulder function, fatigue, fear of movement, and shoulder related quality of life. Patients with mechanical shoulder symptoms were younger (35.1 vs 43.3 years), had longer symptom duration (median 46 vs 24 months), reported a previous shoulder dislocation (25% vs 3%), experienced that their shoulder was loose (64% vs 15%), and reported shoulder discomfort due to mechanical shoulder symptoms (OR 1.48, 95% CI 1.17, 1.87). Furthermore, a larger proportion had received additional treatment (analgesic medication, steroid injection/surgery).

IV) In the RCT, 93 of 100 patients (93%) completed the 16-week evaluation. The between-group difference in the mean WOSI score significantly favoured HEAVY (-174.5 points, 95% CI -341.4, -7.7, adjusted for age, sex, baseline score, clustering around physiotherapy clinics). Patients in HEAVY were less likely to have a shoulder rotation test above 180° and more likely to rate an essential improvement of "physical symptoms" (Global Perceived Effect). However, most secondary outcomes were inconclusive. There were no serious adverse events, but patients in HEAVY reported more transient muscle soreness and headaches. The per-protocol analyses supported the main findings. The clinical relevance of the between-group difference remains unclear.

Conclusions

The HEAVY programme was feasible and tolerable for patients with HSD and persistent shoulder complaints. A high-quality RCT comparing HEAVY and LIGHT programmes was designed, described, initiated, and completed with a final inclusion of 100 patients. At baseline, patients had substantial shoulder related impairments. Two-thirds of the patients reported mechanical shoulder symptoms, and were younger and more severely impaired than those without mechanical shoulder symptoms. These findings highlight the importance of addressing mechanical shoulder symptoms during treatment to understand the patients' shoulder impairments fully. At the primary endpoint 16 weeks postintervention, HEAVY was statistically superior to LIGHT and may be used as treatment in patients with HSD and shoulder complaints to alleviate symptoms and improve shoulder function in the short term. Patients should be supported to manage the associated transient soreness and headaches. However, further studies are needed to confirm the clinical relevance of the between-group difference, to explain the underlying mechanisms, and to evaluate the long-term effectiveness. A high load training protocol may potentially improve clinical practice and treatment of the critical and severe condition of HSD.

Dansk resumé

Introduktion

Hypermobile led er kendetegnet ved en evne til at bevæge leddene ud over den normale bevægelighed. Symptomgivende hypermobile led kaldes hypermobility spectrum disorders (HSD). Fire ud af fem patienter med HSD oplever skulderbesvær, herunder vedvarende smerter og mekaniske skuldersymptomer (instabilitet, subluxation, løshed). Ingen undersøgelser har dog fokuseret på træningsbaseret behandling af skulderen i denne patientgruppe. Styrketræning med høj belastning resulterer generelt i en markant stigning i muskeltværsnittet, det neurale drev, og øget sene stivhed, alle vigtige komponenter for at opnå aktiv skulderstabilitet under bevægelser i hverdagen. Patienter med HSD udviser ofte nedsat styrke og øget skulder løshed/instabilitet og kan derfor sandsynligvis drage fordel af at styrke skuldermusklerne ved hjælp af øvelser med tung belastning. Dette er ikke testet endnu, idet mange klinikere tøver med at bruge tung styrketræning hos patienter med HSD på grund af usikkerhed om patientsikkerhed, behandlingseffekt, og fordi de nuværende retningslinjer fraråder tung styrketræning til denne population.

Formål

Det overordnede mål var at undersøge patienter med HSD og vedvarende skulderbesvær samt effekten af progressiv tung styrketræning som behandling. De specifikke mål var:
I) at undersøge gennemførbarheden af progressiv tung styrketræning i patientgruppen med HSD og vedvarende skulderbesvær.
II) at udvikle og beskrive en studieprotokol med et øvelsesprogram for progressiv tung styrketræning (HEAVY) og let styrketræning (LIGHT) for skulderen, målrettet patienter med HSD.
III) at beskrive patienternes skulderrelaterede funktionsnedsættelser med fokus på forskelle mellem patienter med og uden selvrapporterede mekaniske skulder symptomer.
IV) i et randomiseret kontrolleret forsøg at undersøge effekten af 16-ugers HEAVY program for skulderen sammenlignet med LIGHT (sædvanlig praksis) hos patienter med HSD, der har skulderbesvær. Hovedhypotesen var, at HEAVY er bedre end LIGHT i at forbedre selvrapporteret skulderfunktion.

Metode

I) HSD-patienter gennemgik et 16-ugers HEAVY program for skulderen tre gange ugentligt ved hjælp af øvelser rettet mod de skapulære muskler og rotator cuffen. De primære effektmål var at teste gennemførbarheden af studiet i forhold til foruddefinerede kriterier for udførelse af et høj kvalitet randomiseret kontrolleret

studie (RCT), herunder rekrutteringsraten, testens varighed, deltagernes fastholdelse, komplians, og bivirkninger, foruden deltager og fysioterapeut feedback. Data blev behandlet med deskriptiv statistik og parret t-test.

II) En protokol for et superiority, høj-kvalitets, parallel gruppe, klinisk RCT der sammenligner HEAVY med LIGHT skuldertræning blev designet og beskrevet, herunder overvejelser om forbedrede rekrutteringsmetoder, stikprøvestørrelse og statistiske metoder.

III) Baseret på baseline data indsamlet af eksterne blindede fysioterapeuter blandt de rekrutterede deltagere i RCT'en blev patientgruppen med HSD beskrevet i forhold til sygehistorie, selvrapporterede og objektive egenskaber ved skuldersmerter, ubehag i skulderen på grund af mekaniske skuldersymptomer, skulderfunktion, træthed, frygt for bevægelse, skulderrelateret livskvalitet og tidligere behandling. Mekaniske skuldersymptomer blev defineret som selvrapporteret skulderinstabilitet, subluksation og/eller løshed (klassificeret som Ja/Nej). Data blev behandlet med deskriptiv statistisk og logistisk regression.

IV) Deltagerne blev randomiseret til at modtage et HEAVY eller LIGHT træningsprogram tre gange ugentligt med øvelser rettet mod de skapulære muskler og rotator cuffen. Det primære effektmål var gruppeforskellen ved 16-ugers opfølgning i Western Ontario Shoulder Instability Index (WOSI, 0-2100 bedre til værre), suppleret med sekundære selvrapporterede og objektive udfald. Data blev behandlet med multivariable lineær regression, multivariable logistisk regression, og generaliseret lineær regression.

Resultater

I) Tolv patienter var inkluderet. Rekrutteringsraten var 5,6/måned, varigheden (gennemsnitlig ± SD) 105 ± 9 min, fastholdelse 100%, komplians 83%, og fire deltagere oplevede kortvarig ømhed eller smerte. Deltagerfeedback var positiv, og fysioterapeuter fandt interventionen relevant og anvendelig for patientgruppen.

II) HEAVY programmet bestod af fem skulderøvelser. Ved første besøg, blev der udført en fem repetitions maksimum (RM) test for at estimere 10 RM. De første tre uger bestod af en tilvænningsperiode, der progredierede programmet fra tre sæt af en belastning på 50% af 10 RM i uge et, til 70% af 10 RM i anden uge og til 90% af 10 RM i tredje uge. De efterfølgende seks uger (uge 4-9) indeholdt tre sæt af 10 RM, og fra uge 10-15, var belastningen fire sæt af 8 RM. En restitutionsperiode blev anvendt i uge 16 for at give mulighed for den anabolske respons forud for opfølgningstesten. LIGHT programmet bestod af ni øvelser. Fase 1 (uge 1-4) bestod af isometrisk scapula korrektion; Fase 2 (uge 5-10) var isometriske skulderøvelser i neutral position, og i uge 11-13 en kombination af isometriske og dynamiske øvelser med lille bevægeudslag med elastikmodstand fra en gul TheraBand elastik. I fase 3 (uge 14-16) var øvelserne

dynamiske med små bevægeudslag. Patienter i HEAVY blev superviseret to gange om ugen, og patienter i LIGHT fik supervision tre gange i løbet af de 16-ugers intervention.

III) 67 ud af 100 patienter rapporterede mekaniske skuldersymptomer. Patienter i begge grupper rapporterede funktionsnedsættelser relateret til skuldersmerter, skulder funktion, træthed, frygt for bevægelse og skulderrelateret livskvalitet. Patienter uden mekaniske skuldersymptomer var yngre (35,1 mod 43,3 år), havde længere symptomvarighed (median 46 vs. 24 måneder), rapporterede tidligere at have haft skulderdislokation (25% vs. 3%), oplevede, at deres skulder var løs (64% vs. 15%), og rapporterede ubehag i skulderen på grund af mekaniske skuldersymptomer (OR 1,48, 95% CI 1,17, 1,87). Desuden havde en større andel modtaget tidligere behandling (smertestillende medicin, steroid injektion/kirurgi).

IV) I det randomiserede kliniske studie, gennemførte 93 ud af 100 patienter (93%) 16-ugers evalueringen. Den gennemsnitlige gruppeforskel i WOSI-score favoriserede signifikant HEAVY (-174,5 point, 95% CI -341,4, -7,7, justeret for alder, køn, baseline score, klynge omkring klinik). Patienter i HEAVY var mindre tilbøjelige til at have en positiv skulder rotation test over 180°, og mere tilbøjelige til at vurdere en vigtig forbedring for "fysiske symptomer" (Global Perceived Effect). Men de fleste sekundære effektmål var inkonklusive. Der var ingen alvorlige bivirkninger, men patienter i HEAVY rapporterede hyppigere forbigående muskelømhed og hovedpine. Per protokol-analyserne understøttede de primære resultater. Den kliniske relevans af gruppeforskellen er fortsat uklar.

Konklusion

Patienter med HSD og vedvarende skulderbesvær kunne gennemføre og tolerere progressiv tung styrketræning (HEAVY) målrettet skulderen. Et randomiseret klinisk studie, der sammenlignede HEAVY med LIGHT skuldertræning af høj kvalitet, blev designet, beskrevet, initieret og afsluttet med en endelig inklusion af 100 patienter. Ved baseline havde patienterne betydelige skulderrelaterede funktionsnedsættelser. To-tredjedele af patienterne rapporterede mekaniske skuldersymptomer og var yngre samt mere alvorligt svækkede end dem uden mekaniske skuldersymptomer. Disse resultater understreger vigtigheden af at adressere mekaniske symptomer i skulderen under behandlingen for fuldt ud at forstå patienternes skulderrelaterede funktions-nedsættelser. Da HEAVY var statistisk bedre end LIGHT ved det primær end-point 16 uger efter intervention, kan HEAVY fremover anvendes som behandling til patienter med HSD og skulderbesvær for at lindre symptomer og forbedre skulderfunktionen på kort sigt. Patienterne bør støttes i at håndtere den forbigående muskelømhed og hovedpine, som kan være bivirkninger af HEAVY. Fremtidige studier bør undersøge den kliniske relevans af gruppeforskellen, forklare de underliggende mekanismer, og evaluere langtidseffekten. Progressiv tung styrketræning kan potentielt forbedre klinisk praksis og behandling af den kritiske og alvorlige tilstand af HSD.

Abbreviations

CERT	Consensus on Exercise Reporting Template
CI	Confidence Interval
CIS	Checklist Individual Strength
CONSORT	Consolidated Standards of Reporting Trials
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-Five-Level
GJH	Generalised Joint Hypermobility
GPE	Global Perceived Effect
HEAVY	Progressive high load shoulder strengthening exercise programme
hEDS	Hypermobile Ehlers-Danlos Syndrome
HSD	Hypermobility Spectrum Disorders
IPAQ	International Physical Activity Questionnaire
LIGHT	Low load shoulder strengthening exercise programme (usual care)
MID	Minimal Important Difference
NPRS	Numerical Pain Rating Scale
RCT	Randomised Controlled Trial
REDCap	Research Electronic Data Capture
RM	Repetition Maximum
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
TSK-11	Tampa Scale of Kinesiophobia-11
TIDieR	Template for Intervention Description and Replication
VAS	Visual Analogue Scale
WOSI	Western Ontario Shoulder Instability Index
5PQ	Five-Part Questionnaire

Introduction

Musculoskeletal disorders

The burden of musculoskeletal diseases has a growing impact worldwide, being the leading cause of disability and sick leave across Western countries, besides an increasing problem for individuals and health care systems.[1-5] The vast majority of people with musculoskeletal problems have complaints from the shoulder, knee, and lower back.[6] In Denmark, people with musculoskeletal complaints will usually seek help at private – but tax-financed – general practitioners and get a referral to physiotherapy treatment in private practices, which are (partly) tax-financed and partially self-financed. A Danish population-based registry of 522,000 inhabitants identified that shoulder disorders, which are the focus of this PhD thesis, had an incidence of 14 new contacts to general practitioners per 1,000 inhabitants per year.[7] Furthermore, a recent cross-sectional study reported that the shoulder was the main reason for seeking physiotherapy consultation in Danish primary care in 15.9% of 63,566 patients.[8] A subgroup of people at greater risk of developing symptoms and pain than the general population have hypermobile joints (also called "double-jointed"), corresponding to 30 % of the Danish people.[9]

Joint hypermobility

Definition

Joint hypermobility is characterised by an ability to move the joints beyond the normal range of motion, considering the individual's age, sex, and ethnic background.[10-12] Various case definitions have been described. *Inherent joint hypermobility* is predominantly determined by the laxity or tightness of ligaments. It is associated with alterations in the connective tissue and its three most common structural building proteins: collagen, elastin, and fibrillin.[13] *Acquired laxity* may occur following a traumatic injury that alters the integrity of passive structures stabilising the joint (ligament, capsule, glenoid labrum etc.); and hypermobility may be acquired due to an adaptation to a specific sport and physical activity that requires extreme positions and movements of the joints (e.g., swimming, gymnastics, ballet, and dance). Furthermore, joint hypermobility can affect a single joint or have a more generalised character when present at both the minor and major joints of the four limbs and axial skeleton. The latter is often referred to as generalised joint hypermobility (GJH).[13]

Prevalence

The prevalence of GJH in adults measured clinically varies depending on race, sex, and the criteria used to classify the condition.[10-12] A prevalence between 2% to 57% has been reported.[10-12] However, the most precise estimate concerning the general Danish population is from a recent national survey of 2072 participants using a self-reported

and validated questionnaire called the five-part questionnaire (5PQ) (Table 1) that found a self-reported prevalence of 30% for GJH and 5% for GJH including hypermobility of the shoulder.[9] Compared with non-hypermobile individuals, both groups had higher odds and severity of upper body musculoskeletal symptoms and decreased health-related quality of life.

Classification

The criteria for the classification of GJH remains debatable as there is no consensus among international researchers and experts. Historically, different measures have been used with the trade-off between assessing as many other body parts as possible and having a feasible and quick measure to use as a screening tool in clinical practice. The Beighton score (Figure 1) is currently used in most research and clinical settings to classify GJH (usually with a cut-point of at least 4 or 5). It consists of nine dichotomous joint hypermobility tests, where a tested joint is either hypermobile (score = 1) or not hypermobile (score = 0), with the total score ranging from 0 and 9, and higher scores indicating more joints with joint hypermobility/hyperlaxity.[14, 15]

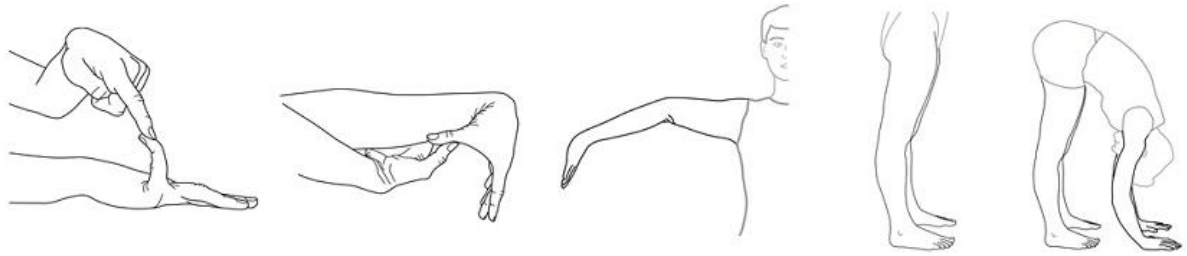

Figure 1. Beighton tests are used to make the clinical classification of generalised joint hypermobility. Passive dorsiflexion and hyperextension of the fifth MCP joint beyond 90°, passive apposition of the thumb to touch the flexor aspect of the forearm, passive hyperextension of the elbow beyond 10°, passive hyperextension of the knee beyond 10°, and active forward flexion of the trunk with the knees fully extended so that the palms of the hands rest flat on the floor. Total score 0-9, with 9 indicating a higher degree of joint hypermobility. Figure courtesy of Dr. Birgit Juul-Kirstensen[16].

Although the Beighton score evaluates a limited number of joints (knee, elbow, fingers, and forward bending), being classified as having GJH by using these tests builds on the assumption that all (or most) joints, including the shoulder, are hypermobile. However, this is an important caveat when using the Beighton score. Therefore, it is recommended to broaden the criteria for classifying GJH and discontinue using a Beighton score below the predefined cut-point to exclude the presence of GJH.[17] To account for this, one possible option is to use the 5PQ (Table 1), which has the strength that it – besides covering questions related to hyperextension of the thumb and forward bending, which are part of the Beighton score – includes additional questions about the childhood, previous abilities, and dislocations of the shoulder and kneecap, thereby using a broader definition and accounting for previous (historical) joint hypermobility. Using a combination of the Beighton score (clinical assessment) and the 5PQ (self-

reported), people with a Beighton score below the cut-point can be classified with GJH if they score above the predefined threshold for the questionnaire. Since the shoulder is not assessed as part of the Beighton score, previous studies have added different measures of shoulder joint hypermobility such as a shoulder external rotation (positive score >90°) with the upper arm in neutral along the side of the body to classify a person as having "GJH including shoulder hypermobility".[18, 19] Other researchers have developed specific hypermobility measures for the upper[20] and lower[21] limbs. The limitation of adding joint-specific measures of hypermobility in symptomatic populations as part of the classification criteria is that the patient may have difficulties performing the tests due to pain and other symptoms (e.g., shoulder apprehension or subluxation). Furthermore, patients may even present with a local hypomobile or stiff shoulder (i.e., decreased range of motion) as a protective or compensatory adaptation to persistent joint complaints, although they are classified as having GJH. Therefore, the current best practice may be to use the Beighton score combined with the 5PQ and consider the patient's overall clinical entity. However, the diagnostic criteria can likely change with more published research on this topic.

Table 1. The five-part questionnaire (5PQ) and an additional shoulder hypermobility question

Question	English version	Danish version	Image
1	Can you now (or could you ever) place your hands flat on the floor without bending your knees?	Kan du nu (eller har du nogensinde tidligere kunnet) nå ned med håndfladerne I gulvet, ved stående forover bøjning uden at bøje i knæene?	
2	Can you now (or could you ever) bend your thumb to touch your forearm?	Kan du nu (eller har du nogensinde tidligere kunnet) bøje din tommelfinger ned så den rører din underarm?	
3	As a child, did you amuse your friends by contorting your body into strange shapes, or could you do the splits?	Kunne du som barn underholde dine venner ved at vride kroppen i opsigtsvækkende stillinger, eller kunne du gå i spagat?	n/a
4	As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?	Gik din skulder eller knæskal af led (ud af sin stilling) gentagne gange, det vil sige mere end én gang, da du var barn eller teenager?	n/a
5	Do you consider yourself double-jointed?	Oplever du dig selv som overbevægelig i dine led (ud over normal ledbevægelighed) sammenlignet med jævnaldrende?	n/a
Shoulder question	Are you hypermobile or loose in one or both of your shoulders?	Er du overbevægelig eller løs i én eller begge dine skuldre?	n/a

A score of at least 2 of the five questions was considered positive for the five-part questionnaire. A score of 1 was accepted for the initial screening of patients if the shoulder question was positive.

Symptomatic joint hypermobility

On the joint hypermobility spectrum, non-symptomatic joint hypermobility may be an advantage in many activities, especially in sports where high flexibility or the ability to maintain extreme positions are required.[22] However, joint hypermobility may be symptomatic where patients present with chronic or recurrent pain, joint sprains, dislocations, subluxations, musculoskeletal problems, fatigue, and disability, resulting in a decreased ability to participate in daily activities, poor health-related quality of life, and increased psychological problems.[22-29]

Hypermobility spectrum disorders (HSD) are a recently defined group of conditions related to symptomatic joint hypermobility, including one or more secondary musculoskeletal manifestations (Figure 2).[30] The HSD are intended to be diagnosed after any of the rare genetic connective tissue disorders, e.g., Ehlers-Danlos syndromes (EDS), are excluded. The HSD criteria are like those of the hypermobile EDS (hEDS), but without fully meeting the new diagnostic criteria for hEDS (e.g., signs of faulty connective tissue throughout the body including skin hyperextensibility, wound healing abnormalities, easy bruising, hernias, and prolapses).[30, 31] Although HSD and hEDS constitute two distinct inherited connective tissue disorders, they significantly overlap in clinical musculoskeletal manifestations and can be considered almost synonymous in clinical practice.[32-35] However, the prevalence of people diagnosed with EDS in Denmark is generally regarded as low (0.02%), so it is unlikely to meet this patient group regularly as a general practitioner or clinical physiotherapist.[36] Besides the musculoskeletal manifestations in HSD, comorbidities related to joint hypermobility comprehend common disorders such as functional gastrointestinal disorders, cardio-respiratory including cardiac dysautonomia conditions, pelvic prolapses, and psychological distress.[30, 37]

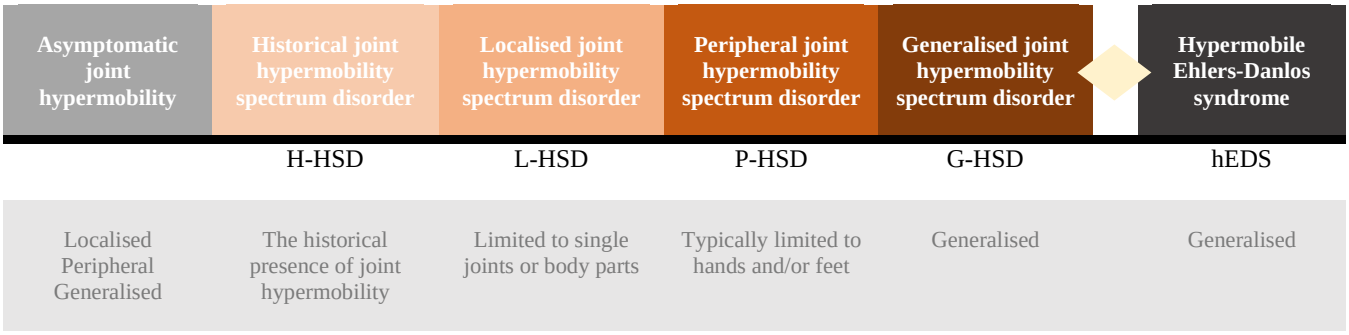

Figure 2. The hypermobility spectrum disorders (HSD).

Joint hypermobility and shoulder complaints

To understand the specific impact of HSD/hEDS on the shoulder, it is important first to appreciate the stabilisation mechanisms of the healthy shoulder. The shoulder is the most mobile joint in the body and is structurally insecure because the large ball-shaped humeral head glides on the shallow glenoid cavity of the scapula.[38, 39] Limited passive

stability is provided by the glenoid labrum, which slightly deepens the cavity, and the ligaments reinforcing the capsule on its anterior and superior surfaces. The humeral head is centered in the glenoid cavity during movements with support from the active system, including the rotator cuff muscles and tendons. Traditionally, shoulder symptoms have been attributed to pathology in various anatomical shoulder structures, such as the rotator cuff muscles and tendons, the coracoacromial ligament, and the capsular or intra-articular tissues. However, most studies show conflicting results on the association between imaging findings and shoulder symptoms.[40] Therefore, the causality of shoulder symptoms has not yet been fully established.

There is strong evidence for the burden of shoulder impairments in people with joint hypermobility, as in HSD/hEDS. Painful shoulder conditions are experienced by at least four out of five patients diagnosed with HSD/hEDS.[41, 42] Besides chronic shoulder pain, patients also report functional shoulder impairments, increased pain intensity, and lower shoulder-related quality of life.[9, 22, 41-43] Furthermore, clinical studies have provided valuable characteristics about this patient group's shoulder biomechanics and muscle-tendon function. Decreased muscle-tendon stiffness is a common finding and thought to be an essential trait; Rombaut et al., 2012, provided the first evidence for altered passive properties of the muscle-tendon unit in the lower leg in patients with hEDS .[44] The authors suggested that the observed changes were possibly related to alterations in the connective tissue. In a more recent study, Alsiri et al., 2019, found decreased musculoskeletal tissue stiffness in the shoulders of patients with HSD using strain elastography, an ultrasound imaging method increasingly used to understand tissue quality.[45] Further, a study by Kjaer et al., 2020, found that patients with hEDS have a larger available subacromial space outlet than healthy individuals, indicating an increased translation between the humeral head and the glenoid cavity during shoulder movement.[46] When the passive stability is decreased (i.e., decreased stiffness and increased translation), more demand is put on the active support, such as the shoulder muscle-tendon complex, to maintain adequate centring and stability of the joint.[38] Spanhove et al., 2020, found altered scapular kinematics (less scapular upward rotation and posterior tilt) and muscle imbalance (higher electromyographic activity of the infraspinatus, middle trapezius, and posterior deltoid muscles) in a subgroup of patients with HSD/hEDS and multidirectional shoulder instability.[47] These findings are further supported by a recent study by Coussens et al., 2021, who reported that upper limb strength (hand grip) and muscle strength endurance of the upper limb and shoulder muscles were similar between patients with HSD and hEDS but significantly lower than healthy controls.[35] Scapula muscle imbalances and strength deficits have also been found in asymptomatic populations with GJH and local shoulder hypermobility.[18, 19] These findings show that potential deficits related to shoulder movement may involve not only the glenohumeral joint but be related to impaired scapular function as well.

Patients with HSD/hEDS commonly report having "other symptoms" such as the experience of shoulder instability, subluxations, or laxity as an adjunct clinical manifestation to chronic shoulder pain,.[27, 41] "Other symptoms" are in this PhD thesis referred to as having "mechanical shoulder symptoms". Mechanical shoulder symptoms may occur involuntarily or voluntarily during arm movements in certain positions, resulting in severe functional impairments, discomfort, and pain.[48] Sometimes, these symptoms are accompanied by a "popping" noise (Figure 3). Some patients with shoulder complaints experience non-positional shoulder instability with the arm in neutral or close to neutral.[48] The experience of mechanical shoulder symptoms is a critical feature in shoulder instability — related to an extensive symptomatic translation of the humeral head relative to the glenoid fossa[49] — characterised by loss of function, discomfort, and pain.[48] The classification of shoulder instability describes a continuum of pathologies based on aetiology (atraumatic or traumatic), direction (from one direction to multidirectional), frequency (single events to recurrent dislocations), and severity (non-structural or structural lesions).[49, 50] Structural loss (e.g., glenoid labrum tear) is considered the leading cause for shoulder instability,[51] [52-54] while abnormal muscle activation patterns are also frequently reported in patients with shoulder instability even with the absence of structural loss.[48, 55, 56] Furthermore, non-symptomatic individuals with shoulder laxity or hypermobility may experience mechanical shoulder symptoms.[18, 19]

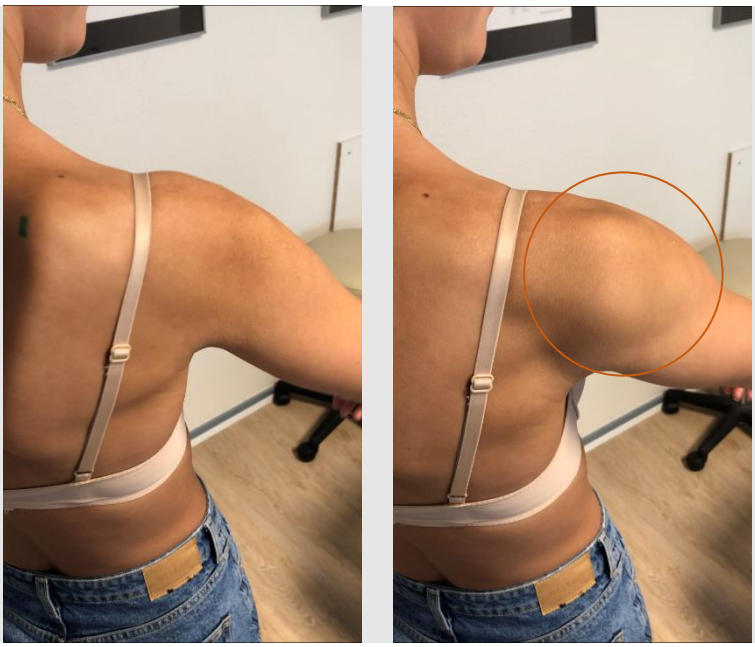

Figure 3. Voluntary subluxation of the shoulder (circle) in a patient with generalised hypermobility spectrum disorder (G-HSD).

No studies have investigated whether mechanical shoulder symptoms are associated with more shoulder-related impairments than not having mechanical shoulder symptoms.

Treatment of shoulder complaints in joint hypermobility

The most recommended treatment for patients with shoulder complaints related to shoulder hypermobility, shoulder instability, and multidirectional instability (MDI) is non-operative, emphasising exercise-based management. However, although patients with HSD/hEDS and shoulder complaints may experience profound consequences in daily living,[23, 24] there is no gold standard treatment for this patient group and no clear consensus.[57]

Current guidelines recommend low load stability exercise and advice about how to protect the joint in daily activities. A closer look at the Danish Rheumatism Association and Arthritis Research UK generally reflects current management in clinical practice: "*In most cases, you can ease your symptoms by doing gentle exercises to strengthen and condition the muscles around the hypermobile joints…"*, and *"The important part is to do these strengthening exercises often and regularly, but not overdo them. Use only small weights, if any...*".[58, 59] Therefore, adults with HSD/hEDS and shoulder complaints will typically receive a treatment that is non-standardised and combines different physiotherapy modalities including passive manual therapy and low-dose exercise prescription.[60-62] However, evidence for these recommendations is sparse and based on theoretical ideas rather than being scientifically proven since no high-quality RCT has investigated the effectiveness of exercise-based interventions in this patient group.[57]

Data from limited randomised controlled trials (RCTs) (Table 2) and uncontrolled studies without long-term follow-up suggest that patients with HSD/hEDS or similar conditions may benefit from structured exercises.[63-76] However, most of these studies did not examine the presence of GJH or shoulder hypermobility, questioning the potential benefits in this patient group.[60, 61, 77, 78] Progressive shoulder exercises to target the scapular stabilising muscles and the rotator cuff muscles have successfully been used for other shoulder complaints, such as rotator cuff tendinopathy, MDI, or following an anterior shoulder dislocation.[63, 64, 79] Furthermore, progressive high load strength training has the potential to reduce pain, increase muscle capacity and tendon stiffness, restore muscle balance and joint proprioception, and improve scapular kinematics during shoulder movement. [44, 65, 80-83] These adaptations are expected to improve active joint stability to compensate for the lack of passive joint stability and positively impact self-reported shoulder function and shoulder-related quality of life, as previously reported for shoulder conditions other than HSD/hEDS.[64, 79, 84]

Therefore, the feasibility, benefits, and harms of progressive high load strength training, such as increased muscle-tendon stiffness and improved shoulder function, should be investigated in patients with HSD/hEDS and shoulder complaints seeking help in primary care.

Summary and rationale for thesis

Even though patients with HSD/hEDS are at increased risk of suffering from shoulder complaints such as chronic pain and mechanical shoulder symptoms, evidence about effective treatment is sparse. Several recent systematic reviews have highlighted the need for rigorous high quality, multi-centre RCTs to investigate the effectiveness of exercise as a treatment for this patient group.[57, 60, 61, 78] Many clinicians use low load strengthening exercises, hesitating to use high load strength training for patients with HSD/hEDS due to uncertainty about patient safety, treatment effectiveness and because current guidelines recommend against high load strength training.[59] However, progressive high load strength training may have the potential to positively impact the many shoulder impairments described on pages 20-21 and be beneficial for self-reported shoulder function and shoulder-related quality of life. Therefore, the feasibility of a progressive high load shoulder strengthening exercise programme should be evaluated and followed by the planning and conduction of a large-scale effectiveness trial using an RCT design. If effective, the recommendation of progressive high load shoulder strength training may provide opportunities for a new treatment strategy.

Table 2. Overview of previous randomised controlled trials on exercise-based treatment in patients with hypermobile and/or unstable shoulders

Author, Year, Country	Participants n; Age mean ± SD or median (IQR)	Inclusion criteria	Intervention	Comparator	Outcomes	Time of interest	Main relevant findings
Warby, 2018[64] Australia	n= 41 Intervention n= 18 (21.8±6.5) Comparator n= 23 (23.0±6.5)	Age range 12-35. Symptomatic glenohumeral joint subluxation or dislocation in >1 direction (positive sulcus sign and a positive drawer or apprehension test). No history of significant trauma to the affected shoulder with confirmation by magnetic resonance imaging to rule out structural lesions of the shoulder.	12-week scapular motor control and rotator cuff/deltoid strengthening exercise programme. Exercises performed per individual functional needs of the patient (every second day or twice a day) and one weekly supervised session of 30 mins. Exercises followed 6 phases, focusing on retraining scapular control and ending with a functional stage. Exercises performed pain-free and progression through stage components achieving pain-free scapular or shoulder motor-control.	12-week strength and stability programme for the rotator cuff, deltoid, and scapula. Exercises performed twice a day with one supervised session of 30 mins per week. Exercises followed 2 phases: phase 1 consisted of 5 exercises with TheraBand resistance (6 levels). Phase 2 consisted of the same exercises but with a 4 kg weight pulley kit, with the progression of 1 kg increments. Exercises performed pain-free, and progression of exercises due to patient-reported "relatively easy" exercise performance.	Melbourne Instability Shoulder Score (MISS) WOSI (0-100, 100 = best) Orebro Musculoskeletal Pain Questionnaire Global Rating of Change Pain, muscle strength, scapular upward rotation, scapular coordinates, global rating of change, satisfaction scales, limiting angle in abduction range, limiting factor in abduction range, and incidence of dislocation.	6 weeks 12 weeks 24 weeks 52 weeks	WOSI total score favoured the intervention group at 12 weeks (MD 11.1, 95% CI 1.9, 20.2, p=0.018) and 24 weeks (MD 12.6, 95% CI 3.4, 21.9, p=0.008). MISS total score favoured the intervention group at 24 weeks (15.4, 95% CI 5.9, 24.8, p=0.002).
Eshoj, 2020[63] Denmark	n= 56 (range, 18-39), Intervention n= 26 (26.2±6.4) Comparator n= 26 (25.8±5.8)	Radiographically verified acute primary or recurrent anterior shoulder dislocation and self-reported decreased ability to perform shoulder movements during daily activities in the previous seven days.	12-week neuromuscular exercise programme targeting the glenohumeral and scapular muscles to increase muscle mass. Supervised sessions twice a week (45 mins) for the first two weeks, then 1 per week for the remaining 10 weeks. Seven exercises performed every day or three times weekly based on level. Exercises progressed through 7 levels (basic to elite) with several progression criteria related to satisfactory neuromuscular control.	12-week standardised care programme reflecting the core similarity of standard care packages – performed three times a week at home. Patients received one supervised physical therapy session with instructions to the home exercises, including an exercise leaflet with photographs and descriptions. Exercises consisted of active exercises for the rotator cuff and scapular muscles with elastic resistance bands and one mobility/coactivation of scapular and core stability muscles. Progression ascertained at 6th week (phone call from physical therapist).	WOSI TSK EuroQol 5-Dimensions questionnaire PSFS Numeric Pain Rating Scale; intensity now, past 24 hours and average pain intensity the previous 7 days Constant-Murley score, Shoulder joint reposition sense Clinical tests for anterior shoulder instability Beighton score Global perceived effect Adverse events	4 weeks 8 weeks 12 weeks	WOSI total score favoured the intervention group at 12 weeks (MD –228.1, 95% CI –430.5, –25.6, p=0.028). A significant difference in favour of the intervention group in the Global perceived effect scale on actual function (p=0.012) and ability to perform sport/leisure activities (p=0.025) at 12-week follow-up.

(*continued on next page*)

Table 2. (*Continued*)

Laudner, 2013[65] USA	n= 41, Intervention n= 24 (19.6±1.8) Comparator n= 17 (18.8±0.9)	No inclusion criteria. Participants were selected based on a sample of convenience. No participants had a recent history (past six months) of upper extremity injury or surgery.	6-week strength and conditioning programme, two sessions a week. Exercises differed during the week, i.e., different exercises during the two sessions. Furthermore, exercises changed for the last two weeks (week 5 and 6). The intervention group continue the standard practice and match schedules besides the intervention programme.	The control group continued standard practice and match schedule but received no exercises.	Anterior shoulder laxity (mm) Anterior Glenohumeral Joint Stiffness (N/mm)	6 weeks	Anterior shoulder laxity favoured the intervention group from baseline to 6 weeks (2.0 vs -1.8 mm, p=0.03). Anterior glenohumeral joint stiffness favoured the intervention group from baseline to 6 weeks (0.01 vs 0.8 N/mm, p=0.03).
Spanhove, 2021[66] Belgium	n= 21 Intervention n= 11 (29(25)) Comparator n= 10 (33.5(35))	Age range 18-65. hEDS or generalised HSD diagnosis according to the 2017 classification of the international EDS consortium. Patients also needed to have MDI confirmed by clinical examination.	24-week tailored home-based exercise programme based on recent HSD/hEDS research data. Exercise booklet and videos were provided. Exercises are divided into four types: shrug, external rotation, bench slides, and wall slides. Exercises had three levels A, B and C (easiest to hardest difficulty) in three phases; phase 1 (baseline to week 12), all patients solely performed A-level exercises daily. Phase 2 (week 13-18) patients completed levels A and B exercises five times a week. Phase 3 (week 19-24) consisted of performing level C exercises as well, with at least three sessions a week. Patients were advised not to continue with exercises if shoulder pain during exercise exceeded 5/10 on a numeric pain rating scale.	24-week standardised home-based exercise programme reflecting evidence-based standard care, in a telerehabilitation format. Exercises are divided into four types: balance and proprioception, isometric strength, rotator cuff muscles, and open chain elevation. Exercises had three levels A, B and C (easiest to hardest). At baseline, patients received a fixed exercise schedule. Still, the exercise plan got altered during weekly telephone conversations if patients could not perform the planned exercises (shoulder pain >5/10 on a numeric pain rating scale or poor exercise quality). Alterations could include a decrease in the number of repetitions, change of exercise level, omission, or replacement by another exercise (if the patient only performed one exercise).	WOSI DASH TSK PSFS The Global Ranting of Change	6 weeks 12 weeks 24 weeks	No significant difference in total WOSI score between groups (p=0.69), but the main effect for time (p=0.019). Significant decrease in total WOSI score at 12 weeks (MD 240 (CI 27.6, 452.8) p=0.019) and 24 weeks (MD 325 (CI 112, 538) p= 0.001) when compared to baseline.

Abbreviations: DASH, The Disabilities of the Arm, Shoulder and Hand; GJH, Generalised Joint Hypermobility; hEDS, hypermobile Ehlers-Danlos Syndrome; HSD, Hypermobility Spectrum Disorders; MD, Mean Difference; MISS, Melbourne Instability Shoulder Score; PSFS, Patient-Specific Functional Scale; TSK, Tampa Scale of Kinesiophobia; WOSI, Western Ontario Shoulder Index.

Aims

The overall aim of the thesis

To investigate patients with joint hypermobility (HSD/hEDS) and persistent shoulder complaints and the effectiveness of progressive high load strength training as treatment.

The specific study aims

I. To investigate the feasibility of using progressive high load strength training in treating patients with HSD/hEDS and persistent shoulder complaints.

II. To develop a well-described study protocol including 16 weeks of supervised progressive high load shoulder strength training (HEAVY) and less supervised, less progressive low load shoulder strengthening exercise (LIGHT).

III. To investigate the severity of functional impairments in patients with HSD/HEDS and persistent shoulder complaints, focusing on subgroups with or without self-reported mechanical shoulder symptoms (subluxation, instability, laxity).

IV. To investigate the short-term effectiveness of progressive high load strength training on shoulder pain, function, and quality of life as a treatment for patients with HSD/hEDS and persistent shoulder complaints using an RCT design. The main hypothesis was that HEAVY is superior to LIGHT in improving self-reported shoulder function.

Method

The methods of the individual studies are presented here, and the method sections of the appended papers can supply further details. There will be some overlap between the studies, and any differences will be highlighted. Paper III used baseline data from the RCT (Paper IV), why the population was the same (Figure 4).

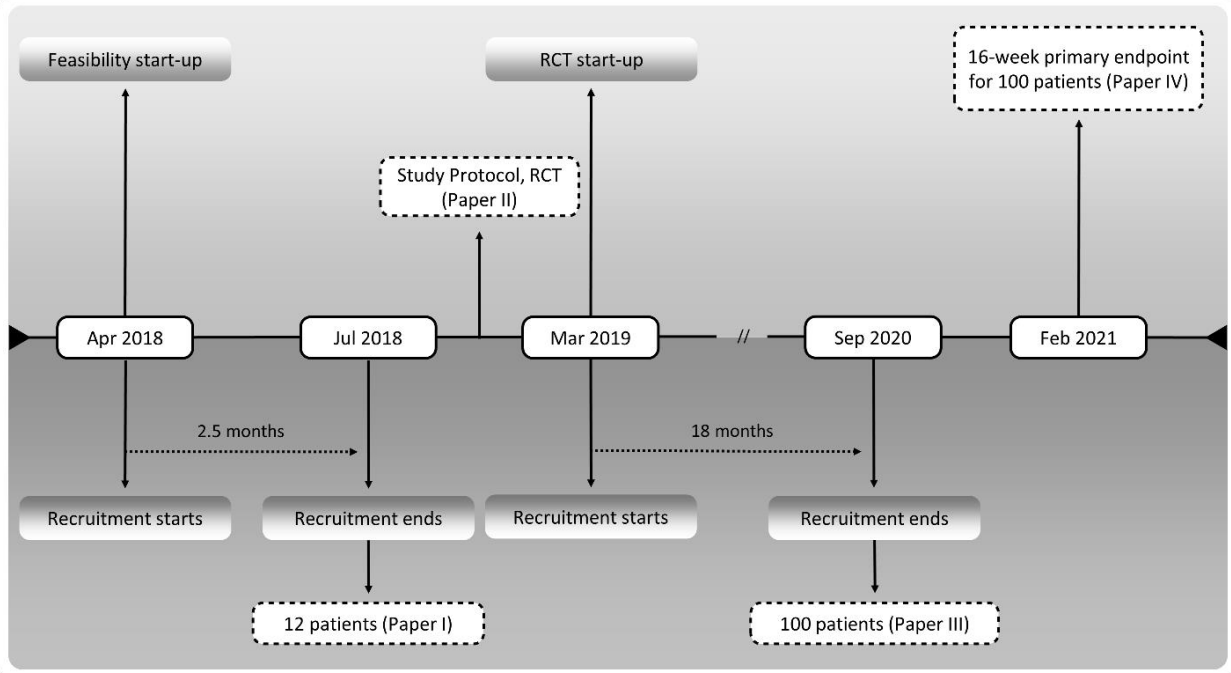

Figure 4 . Overview of the timing of studies and essential highlights in the PhD thesis.

Ethics

Paper I-IV

This PhD thesis was approved by the Regional Committees on Health Research Ethics for Southern Denmark (31 May 2017, S-20170066) and conducted according to the Danish legislation on ethics and the local ethics committee's requirements. The project followed the Declaration of Helsinki[85], was approved by the Danish Data Protection Agency (15 Feb 2018, 17/36907) and the Committee of Multipractice Studies in General Practice in Denmark (12 Feb 2018, MPU 15-2017), and it adheres to the requirements of the Danish Act concerning Processing of Personal Data.

All included patients (n = 112) were informed about the process, the potential risks, that they could withdraw from the study at any point in time, and that they would not receive any financial compensation but get all treatment expenses covered by the

project. All patients were asked to give their written informed consent before enrolment in the studies.

To design high-quality research trials, and in respect of the patients included, all relevant guidelines were followed related to the protocol design, registration, completion, and reporting. Furthermore, for the RCT, a blinded interpretation of the findings that all authors signed was submitted online before breaking the randomisation code.

Clinicaltrials.gov was used to prospectively register the feasibility study (Paper I, NCT03547570, registered on 3 May 2018) and the RCT (Paper II-IV, NCT03869307, registered on 11 March 2019) to ensure transparency before initiating the studies. Statistical analysis plans were published to reduce bias with the Open Science Framework a priori for Paper III (19 Dec 2020, https://osf.io/pvnku/) and Paper IV (9 Jun 2021 https://osf.io/afgn2/).

In the protocol design, the interventions were standardised and described according to the template for intervention description and replication (TIDieR)[86] checklist, the Consensus on Exercise Reporting Template (CERT)[87], and a mechano-biological description as recommended by Toigo and Boutellier[88].

Reporting of the papers was conducted according to the CONSORT statement extension to randomised pilot and feasibility trials (Paper I),[89] the STROBE guidelines for cross-sectional studies (Paper III), and the CONSORT guidelines for reporting parallel group randomised trials (Paper IV). Embedded in initiating the RCT was developing a study protocol, which adhered to the PREPARE Trial guide[90] and the SPIRIT checklist[91] and was published (Paper II).

Study design

Paper I-IV

As outlined in the following paragraphs, three different study designs were used in this PhD thesis.

Paper I was a feasibility study to evaluate predefined research progression criteria in preparation of the definitive parallel-group RCT (Paper II-IV). No comparator or randomisation was used since most of these criteria except the recruitment rate were related to the experimental intervention alone. The research progression criteria were defined using a traffic light system of green (initiate an RCT without changes), amber (apply changes to improve study design), and red (no RCT unless significant changes are applied).[92] For practical reasons, the principal investigator (BL) performed the outcome assessments of this feasibility study semi-blinded since no access was given to the baseline values until after the follow-up assessments were completed. Blinding was

unnecessary because the focus was on evaluating the progression criteria and not the secondary self-reported and objective measures.

Paper II was a protocol paper for the complete RCT, which is essential because it pre-specified the trial's important aspects, such as the methods and the primary outcome. Having a published protocol helps restrict the likelihood of undeclared changes and report selective outcomes. The protocol was published in an open-access journal to make it easily accessible.

Paper III was a descriptive study using baseline data from the RCT to investigate and further detail the clinical characteristics of the included patients, with a particular focus on self-reported mechanical shoulder symptoms.

Paper IV, the main study of this PhD thesis, was the assessor-blinded, multicenter, superiority, RCT with a two-group parallel design, comparing HEAVY with LIGHT (considered usual care in Denmark) programmes. Patients were randomised with a 1:1 allocation ratio, without an option to cross over. The primary endpoint was the between-group difference in self-reported shoulder function at 16-week follow-up.

Setting

Paper I-IV

The clinical studies (Paper I, II and IV) were conducted in the primary care in Odense, Middelfart, and Esbjerg within the Region of Southern Denmark, which with its approx. 1.2 million people (21%) represent Denmark's general patient population (Figure 5).

Figure 5. The clinical studies were conducted in primary care in the cities of Odense, Middelfart, and Esbjerg within the Region of Southern Denmark, representing a general patient population in Denmark.

Participants

Paper I-IV

The eligibility criteria used in this PhD thesis align with the overall recommendations from an international consensus paper by Castori et al., 2017.[30] Patients with persistent shoulder complaints were included if they met the predefined eligibility criteria for actual or historical HSD, which further included having symptomatic GJH with musculoskeletal manifestations. Patients with GJH (actual/historical) were included using a combination of the Beighton tests, with a predefined cut-point of 4 or 5, and the 5PQ questionnaire with a cut-point of at least 2 (Table 3). Musculoskeletal manifestations were defined as chronic shoulder pain for at least three months and/or trauma/orthopaedic traits, referring to self-reported dislocations, subluxations, and instabilities (Table 3).[30] Patients with two of the other four sub-classifications of HSD (Peripheral-HSD and Local-HSD) were intentionally not included in this PhD thesis to avoid patients with acquired local shoulder hypermobility only.

Table 3. Eligibility criteria for patients in the clinical studies (Paper I, II, and IV)

Inclusion criteria	**Exclusion criteria**
Males and females aged between 18 and 65 years. Generalised HSD (G-HSD) defined using a Beighton score cut off ≥ 5/9 for females up to the age of 50 years, and ≥ 4/9 for those > 50 years and all males[31], or Historical HSD (H-HSD) if the Beighton score is 1 point below the age and sex-specific cut off and the 5PQ is positive (≥ 2/5 positive answers).[93] One or more of the following self-reported (yes/no) symptomatic musculoskeletal manifestations present.[30, 31] - Chronic pain (musculoskeletal pain in at least one shoulder for at least three months). - Trauma and/or orthopaedic traits: recurrent joint dislocations or joint instability without a reported history of trauma defined as (a) a minimum of three atraumatic dislocations in the affected shoulder, (b) a minimum of two atraumatic dislocations in two different joints (a minimum of one in the shoulder) occurring at different times, and/or (c) medical confirmation of joint instability in at least two joints (a minimum of one in the affected shoulder).	Clinically suspected referred pain from the cervical spine. Diagnosis of systemic inflammatory rheumatic diseases, connective tissue diseases (e.g., Marfans, Stickler's or Loeys Dietz syndromes, EDS except for hypermobile type EDS), and/or neurological disorders. Pregnancy or childbirth within the past year or planning to get pregnant during the study period because of increased relaxin levels. Shoulder surgery within the past year. Steroid injection in the affected shoulder in the previous three months. Inability to speak or understand Danish. Inability to comply with the study protocol. Inability to provide informed consent.

Abbreviations: 5PQ, Five-Part Questionnaire; HSD, Hypermobility Spectrum Disorders; EDS, Ehlers-Danlos Syndrome.

Patients with hEDS were expected to have a formal medical diagnosis prior to participation in the studies, besides fulfilling the criteria for GJH and musculoskeletal manifestations. However, it turned out that none of the included patients had a diagnosis of hEDS.

Procedure and data collection

Paper I-IV

Patients with shoulder complaints were asked to answer an online pre-screening questionnaire specifically designed for this project. The questionnaire included the 5PQ, a quick self-reported measure of GJH, and questions about the duration of shoulder complaints, through the data management software Research Electronic Data Capture (REDCap). The principal investigator (BL) contacted patients considered potentially eligible (i.e., having shoulder complaints plus 5PQ ≥ 2 or 5PQ = 1 and self-reported hypermobile shoulder) for a physical screening using the Beighton tests[16] to make a clinical diagnosis of HSD/hEDS. A project manager at the University of Southern Denmark was responsible for randomisation procedures and practical management of the project. She was not otherwise involved in the project. The baseline and follow-up assessments were completed at two sites (Esbjerg Municipality Rehabilitation Centre, Esbjerg, Denmark, and the Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark) by one of four blinded physiotherapists who were not otherwise engaged in the project. The study interventions were delivered at a physiotherapy clinic close to the patients´ home by one of five (Paper I) and 23 (Paper IV) treating physiotherapists, who had undergone a 3-hour theoretical and practical education programme supported with a manual with detailed exercise instructions and the option to contact the principal investigator with questions. Home-based exercises for both groups took place with no physiotherapist and outside the physiotherapy clinics (e.g., in the patient's home). The project covered all treatment expenses for both groups.

Intervention

Paper I, II, IV

A progressive high load shoulder strength training programme, HEAVY (Table 4), was developed and tested using an open kinetic chain and full range exercises (Paper I and II). The same HEAVY programme was used in the RCT (Paper IV) since no changes were deemed necessary following the feasibility study outcomes (see results section, p. 55). For 16 weeks, patients were individually supervised twice a week at a physiotherapy clinic (60 min for the first session, 30 min for the following sessions) and exercised once a week non-supervised at home or self-selected location. The exercise programme included five scapular and rotator cuff muscles exercises using regular dumbbells (2–15 kg) in the feasibility study (Paper I). In the RCT (Paper IV), additional custom-made adjustable 3D-printed dumbbells (0–1000 g) were used to allow for adjustments with 50g intervals (see page 39).

The exercises were side-lying external rotation (ER) in neutral (Figure 6), prone horizontal abduction (Figure 7), seated shoulder elevation in the scapular plane (Figure 8), prone ER at 90° of shoulder abduction (Figure 9), and supine scapular protraction (Figure 10). A 5-repetition maximum (RM) test was carried out at the first session to estimate the 10 RM using Brzycki's formula.[94] The first three weeks consisted of a familiarisation period progressing from three sets of a load of 50% of 10 RM in week one, 70% of 10 RM in the second week, and 90% of 10 RM in the third week. The following six weeks (weeks 4–9) included three sets of 10 RM, and from weeks 10–15, the training load was four sets of 8 RM. A tapering period was applied in week 16 to allow the anabolic response before follow-up testing. Each exercise session consisted of 5 min of warm-up (performing the exercises unloaded), and patients received education in scapular correction and general advice on joint protection adapted by the Danish Rheumatism Association.[59]

Table 4. Mechano-biological description of the progressive heavy shoulder strengthening exercise programme (HEAVY).[88] This table is reused from Paper II

Week	X_1	X_2	X_3	X_4	X_5	X_6	X_7	X_8	X_9	X_{10}	X_{11}	X_{12}	X_{13}
1	50% 10 RM	10	3	60 s	3 per week	1 week	3 s shortening 0 s isometric 3 s lengthening	0 s	60 s	No	Full ROM	48 h	Yes
2	70% 10 RM	10	3	60 s	3 per week	1 week	3 s shortening 0 s isometric 3 s lengthening	0 s	60 s	No	Full ROM	48 h	Yes
3	90% 10 RM	10	3	60 s	3 per week	1 week	3 s shortening 0 s isometric 3 s lengthening	0 s	60 s	No	Full ROM	48 h	Yes
4	10 RM	10	3	60 s	3 per week	6 weeks	3 s shortening 0 s isometric 3 s lengthening	0 s	60 s	Yes	Full ROM	48 h	Yes
10	8 RM	8	4	90 s	3 per week	6 weeks	3 s shortening 0 s isometric 3 s lengthening	0 s	48 s	Yes	Full ROM	48 h	Yes
16	70% 8 RM	8	4	90 s	3 per week	1 week	3 s shortening 0 s isometric 3 s lengthening	0s	48 s	No	Full ROM	48 h	Yes

X_1 load magnitude, X_2 number of repetitions, X_3 number of sets, X_4 rest in-between sets, X_5 number of sessions per week, X_6 duration of the experimental period, X_7 fractional and temporal distribution of the contraction modes per repetition and duration of one repetition, X_8 rest in between repetitions, X_9 time under tension (s), X_{10} volitional muscular failure, X_{11} range of motion, X_{12} recovery time in between exercise sessions, X_{13} predefined anatomical exercise form.

Figure 6. High load exercise 1: side-lying external rotation. Start position (A) and end position (B). Instruction: "Stabilise the shoulder blade by lifting the shoulder slightly towards the ear while moving the shoulder slightly down/back towards the spine. Upwardly rotate the arm while holding the upper arm close to the body. Slowly lower the arm." This image is reused from Paper I.

Figure 7. High load exercise 2: prone arm raise with external rotation. Start position (A) and end position (B). Instruction: "Stabilise the shoulder blade by lifting the shoulder slightly towards the ear while moving the shoulder slightly down/back towards the spine. Lift the arm straight out to the side up to the horizontal as you turn the arm/hand outwards. When you reach the horizontal position, externally rotate the hand further. Lower the arm slowly while returning it to the starting position." This image is reused from Paper I.

Figure 8. High load exercise 3: seated scaption (arm lift obliquely forward). Start position (A) and end position (B). Instruction: "- Stabilise the shoulder blade by placing the opposite hand's index finger and middle finger behind the back underneath the shoulder blade and then moving the bony point backwards and away from the fingers. Activate the deep stabilising back muscles by exhaling with the mouth closed (and the teeth clenched together). Lift the arm obliquely forward and up. Lower the arm slowly". This image is reused from Paper I.

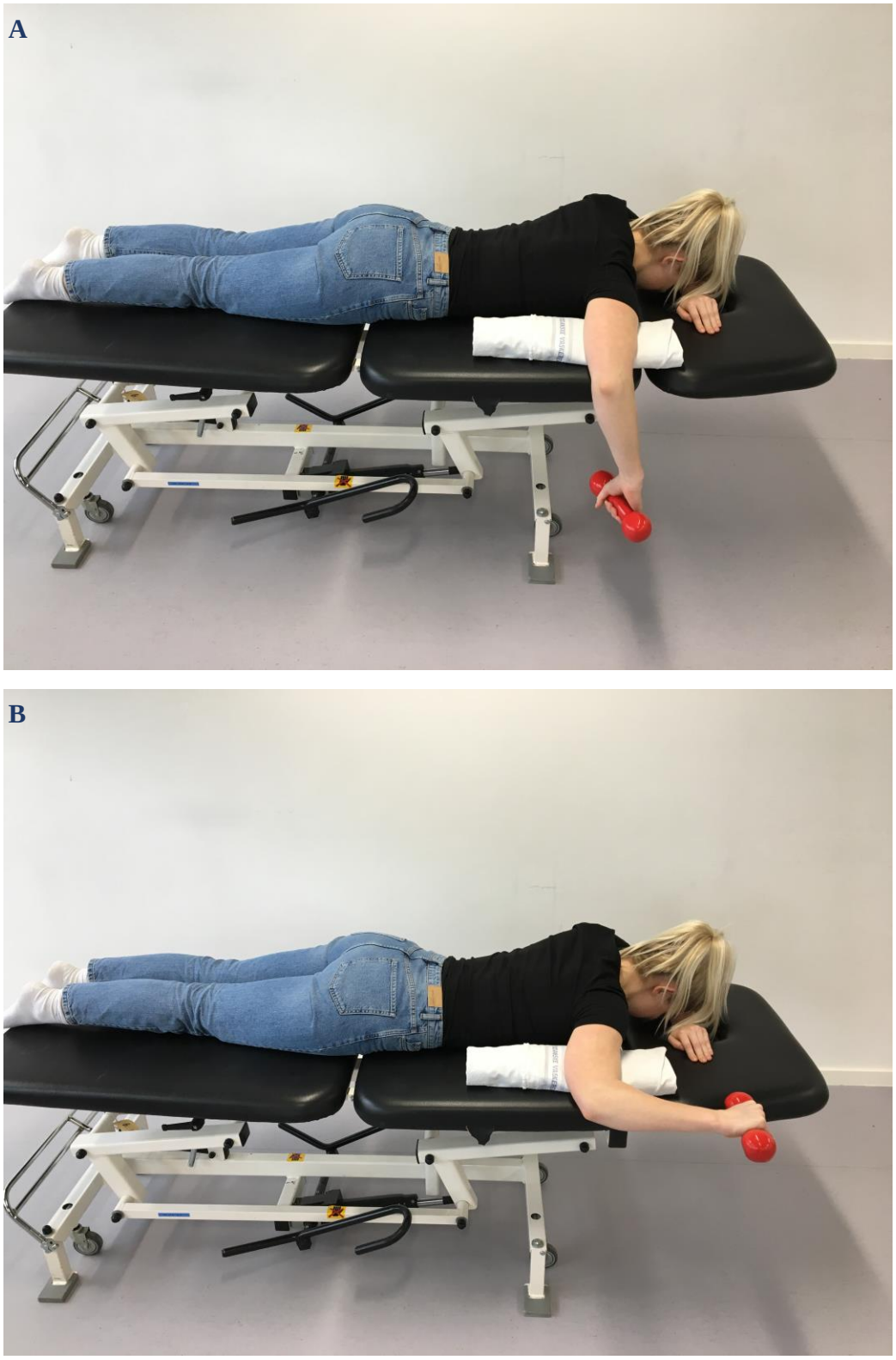

Figure 9. High load exercise 4: prone external rotation with shoulder and elbow at 90°. Start position (A) and end position (B). Instruction: "Stabilise the shoulder blade by lifting the shoulder slightly towards the ear while moving the shoulder slightly down/back towards the spine. Turn the forearm up towards the ceiling. Lower it again slowly." This image is reused from Paper I.

Figure 10. High load exercise 5: supine scapula protraction (push with arm). Start position (A) and end position (B). Instruction: "Press the stretched arm up towards the ceiling to extend the arm, and the shoulder is no longer supported. Slowly lower the shoulder again, so it comes down to touch the supporting surface. Ensure that the shoulder is not pulled up against the ear and that the arm is pressed straight up towards the ceiling." This image is reused from Paper I.

Development of adjustable 3D-printed dumbbell

Paper II

From patient and physiotherapist feedback in the feasibility study (Paper I), there was a need to develop a better solution for providing resistance during the exercises. Since the regular dumbbell without weight plates weighed 2 kgs, patients had to use the weight plates without the dumbbell when they needed resistance less than 2 kgs. This was uncomfortable for their hands and fingers. Furthermore, the standard weight plates only allowed adjustments with 500 g intervals. Therefore, an adjustable 3D-printed dumbbell (Figure 11) was developed for the RCT (Paper IV) in collaboration with Mads Nygaard, Fablab UCL, University College Lillebaelt, Odense, Denmark.

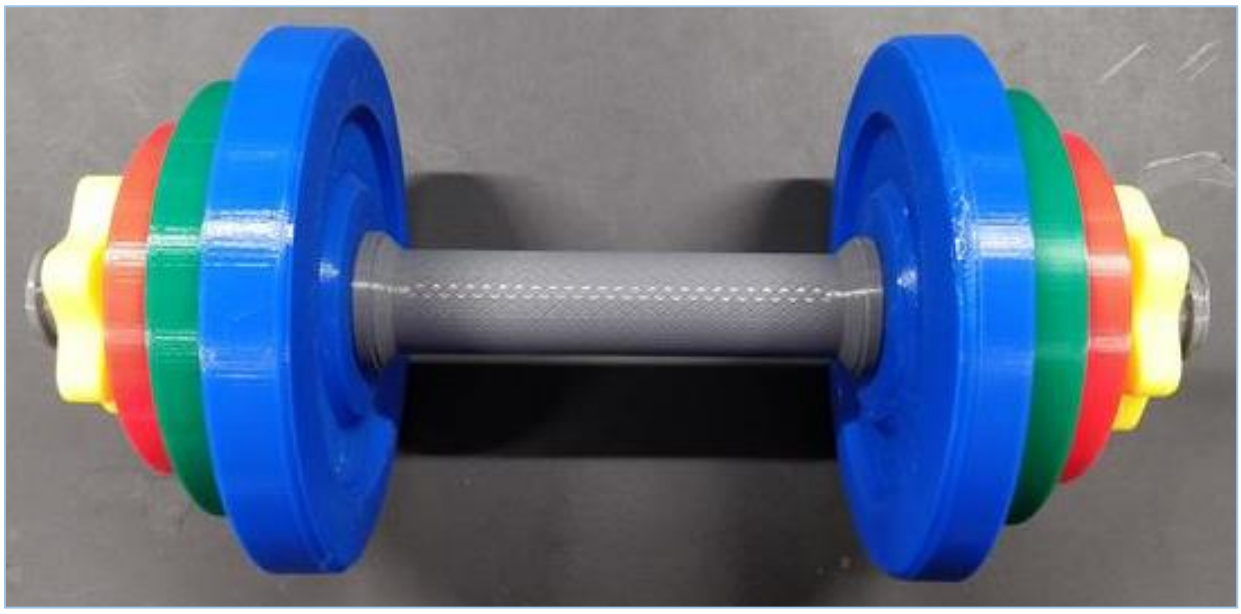

Figure 11. A 3D-printed dumbbell was designed (Paper II) for the randomised controlled trial (Paper IV) to allow minor adjustments with 50g intervals in the progressive high load strengthening exercise programme.

Load progression criteria

Paper I, II, IV

The exercise load was continuously adjusted to the increased or decreased capabilities of the patients. Criteria for an increase were whenever the patient could complete more than the predefined repetitions for all sets with acceptable symptoms below 5/10 on a numerical pain rating scale (self-reported) and scapular stability (objectively evaluated by the treating physiotherapist) during the exercise. The scapular stability was compared with unloaded movement and defined as no obvious winging or pseudo winging, controlled and coordinated upward and downward rotation of the scapula, and no noise or 'gives' (i.e., subluxation) in the glenohumeral joint. In case that patients

experienced symptoms or pain flares above the acceptable threshold for more than 2–3 hours, e.g., until the next day or the next exercise session, the exercises were modified (Figure 12). The exercises were then performed at that level until the symptoms decreased below the acceptable threshold. After that, load increases would follow the progression as initially planned. For patients with symptoms at rest above 5/10 at baseline, no increase in symptoms would be allowed during exercise.

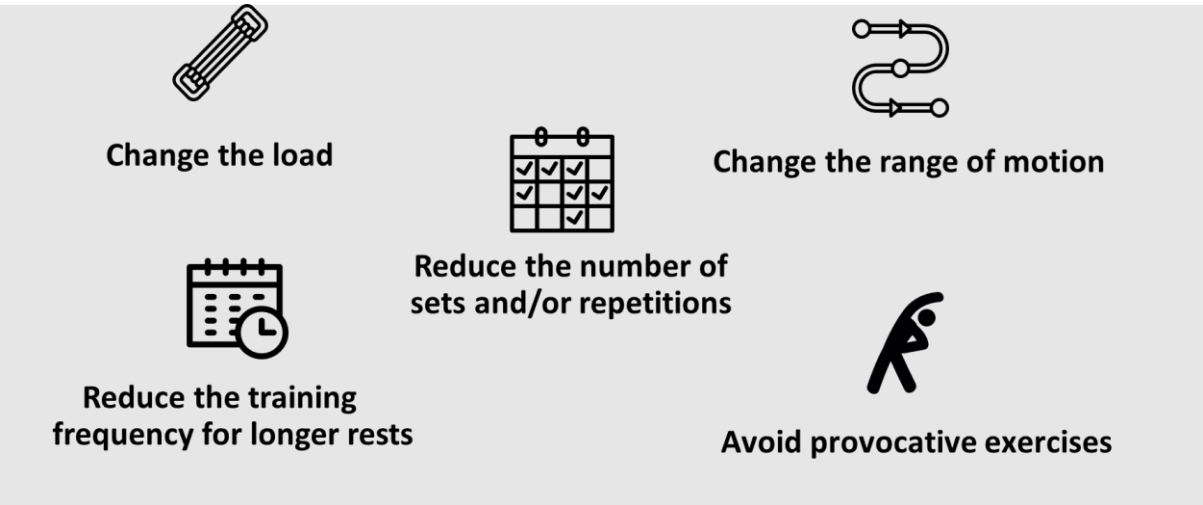

Figure 12. Modification factors when patients experienced unacceptable symptoms or pain flares above the threshold of 5/10 on a numerical pain rating scale that lasted for more than 2–3 hours, e.g., until the next day or the next exercise session. It was up to the treating physiotherapist in collaboration with the patient to decide how the exercises were modified.

Comparator

Paper II, IV

An active control, LIGHT (Table 5), was developed (Paper II) for the RCT (Paper IV) to mimic usual care of patients with HSD and shoulder complaints in Denmark and internationally.[62] An active comparator was used based on the current clinical recommendations, consisting of advice about joint protection, prescription of exercises with low load, and education about the condition from the physiotherapist.[58, 59, 78]

Patients received an individual face-to-face introduction to the exercises before initiating the programme and individual supervision (30 min per session) at weeks 5 and 11 when they started with new exercises. The exercise programme included nine exercises for scapular and rotator cuff muscles and tendons (Figure 13): phase 1 (isometric), posture correction; phase 2 (isometric), shoulder abduction, shoulder internal and external rotation with 90° flexion at the elbow joint and standing weight-bearing in the shoulders against a table; and phase 3 (dynamic with resistance band),

shoulder abduction, shoulder internal and external rotation at 90° flexion at the elbow joint, and four-point kneeling with single arm raising. The first four weeks consisted of the phase 1 exercise, with a set of 10 repetitions (10 s hold per repetition). The following six weeks (weeks 5–10) consist of isometric exercises from phase 2 with two sets of 10 repetitions (2–3 s hold). In weeks 11–13, the exercises included a combination of phase 2 and phase 3 with one set of 10 repetitions from each phase. In weeks 14–16, the exercises were dynamic from phase 3 with two sets of 10 repetitions. Exercises were performed with or without a TheraBand resistance band, and the patients managed the load by the written instructions.

Table 5. Mechano-biological description of the low load exercise programme (LIGHT).[88] This table is reused from Paper II

Week	**X_1**	**X_2**	**X_3**	**X_4**	**X_5**	**X_6**	**X_7**	**X_8**	**X_9**	**X_{10}**	**X_{11}**	**X_{12}**	**X_{13}**
1	Isometric load	10	1	0 s	3 per week	4 weeks	10 s isometric	0 s	100 s	No	Neutral	48 h	Yes
5	Isometric load	10	2	30 s	3 per week	6 weeks	2-3 s isometric	0 s	60 s	No	Neutral	48 h	Yes
11	Isometric load	10	1	30 s	3 per week	3 weeks	2-3 s isometric	0 s	60 s	No	Neutral	48 h	Yes
11	Dynamic Light (yellow) resistance band	10	1	30 s	3 per week	3 weeks	3 s shortening 0 s isometric 3 s lengthening	0 s	60 s	No	Mid-range	48 h	Yes
14	Dynamic Light (yellow) resistance band	10	2	30 s	3 per week	3 weeks	3 s shortening 0 s isometric 3 s lengthening	0 s	60 s	No	Mid-range	48 h	Yes

X_1 load magnitude, X_2 number of repetitions, X_3 number of sets, X_4 rest in-between sets, X_5 number of sessions per week, X_6 duration of the experimental period, X_7 fractional and temporal distribution of the contraction modes per repetition and duration of one repetition, X_8 rest in between repetitions, X_9 time under tension, X_{10} volitional muscular failure, X_{11} range of motion, X_{12} recovery time in between exercise sessions,
X_{13} predefined anatomical exercise form.

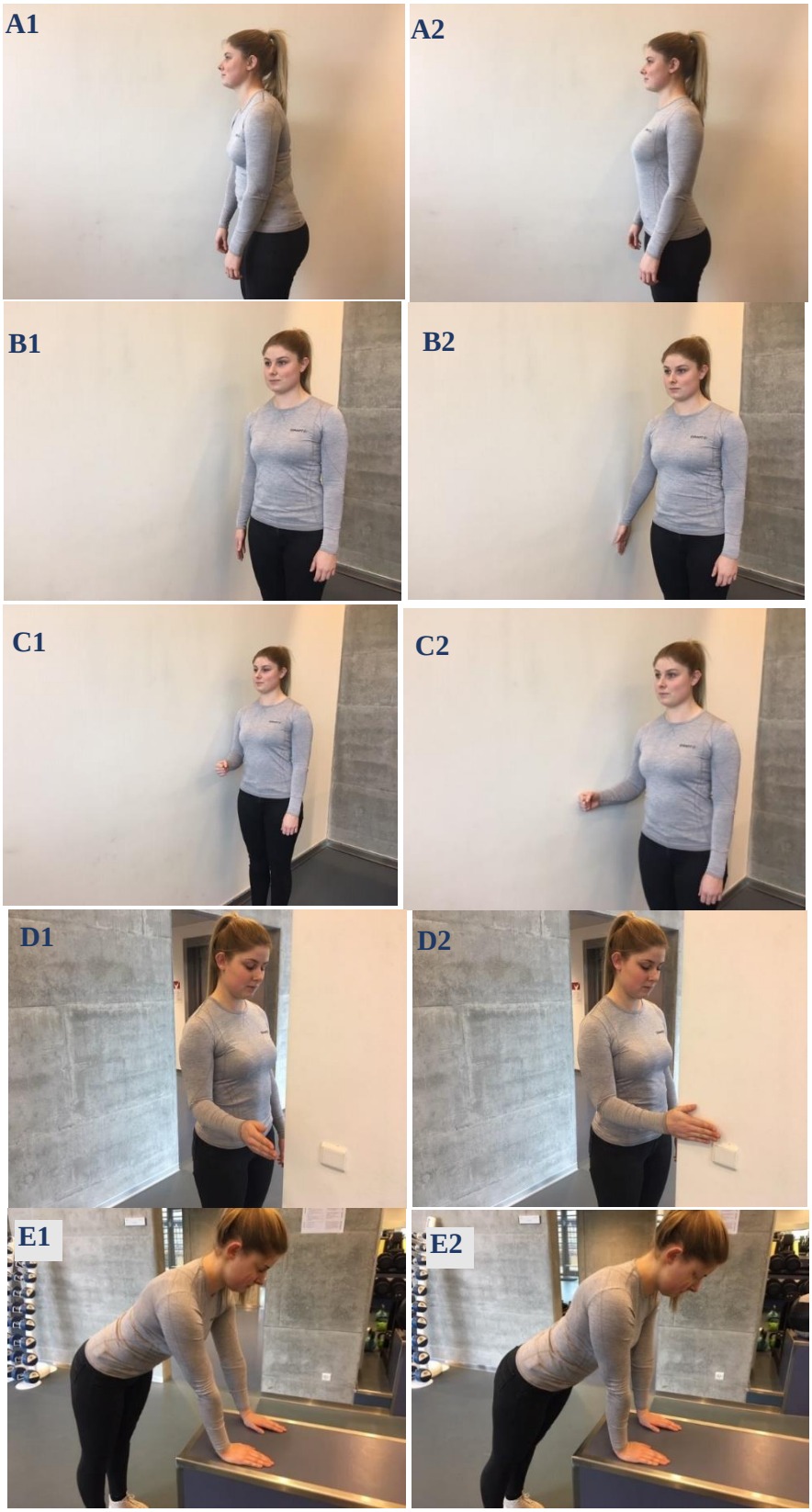

Figure 13. Low load exercises. A1-A2: Posture upright, B1-B2: Abduction (static), C1-C2: External rotation (static), D1-D2: Inward rotation (static), E1-E2: Push up (static), F1-F2: Abduction (dynamic), G1-G2: External rotation (dynamic), H1-H2: Inward rotation (dynamic), I1-I2: Arm flexion in four-point kneeling.

Figure 13. (Continued) Low load exercises. A1-A2: Posture upright, B1-B2: Abduction (static), C1-C2: External rotation (static), D1-D2: Inward rotation (static), E1-E2: Push up (static), F1-F2: Abduction (dynamic), G1-G2: External rotation (dynamic), H1-H2: Inward rotation (dynamic), I1-I2: Arm flexion in four-point kneeling. This figure is reused from Paper II.

Outcomes

Research progression criteria

Paper I

The feasibility study used a mixed outcome approach based on primary outcomes including predefined research progression criteria (Table 6), qualitative feedback from patients and physiotherapists, and a range of secondary self-reported outcomes and objective measurements to cover most aspects of potential benefits and identify outcomes which were responsive to the intervention. General demographic information was also obtained and included sex, age, weight, height, civil status, educational level, employment status, disease history and physical activity level (high, moderate, or low) using the short version of the International Physical Activity Questionnaire (IPAQ).

Recruitment procedures were evaluated by comparing the number of patients at pre-screening with patients eligible for inclusion to identify reasons for exclusion and optimise the eligibility criteria. The recruitment rate was analysed by dividing the number of included patients (n=12) by the number of months it took to include them (calculated from the study start until the 12th patient was recruited). To evaluate the duration of baseline and follow-up assessment sessions, completion was timed, and patients were asked if they found the duration acceptable (yes/no). Patient retention was evaluated by the number of patients showing up at 16-week follow up. To evaluate exercise adherence, which was calculated as the number of completed sessions, exercise logs were filled out at each session by both the patient (at home) and the physiotherapist (when supervised), covering pain before and after exercise, load and intensity, and pain medication use.

Adverse events

Paper I, II, IV

In Paper I, the investigators evaluated the adverse events and decided on the amendments needed based on the research progression criteria (Table 6). Adverse events were registered at every exercise session and at follow-up. Furthermore, patients received an electronic questionnaire by email every week with questions about adverse events, pain levels, sickness absence, and use of pain medication and additional healthcare treatment. Minor adverse events covered symptom flare-up, subluxations, and post-exercise fatigue. Serious adverse events were unexpected but covered life-threatening events, disability, and permanent damage.[95]

Patient and physiotherapist involvement

Paper I

It is recommended to involve patients and other relevant stakeholders to improve both the methodology and outcomes of research projects.[96] Therefore, patients from the feasibility study were asked to provide feedback at 16-week follow up on a custom-made questionnaire with open questions on acceptability of assessment procedures, previous treatment experience compared with high load shoulder strengthening exercise, and feedback about the supervised sessions and potential adverse events. Physiotherapists were asked whether exercises were applicable to this patient group and their experience with using the exercise manual, including handling the progression of exercise intensity and exercise and load modification in case of pain flare-ups or other adverse events. Both patients and physiotherapists were asked to suggest potential improvements for the study design and procedures as part of the overall evaluation.

Table 6. Research progression criteria for continuing to the definitive randomised controlled trial (Study 1). This table is modified from Paper I

Outcome	Green	Amber	Red
Patient recruitment	The inclusion rate of one patient per general practitioner or physiotherapist every month (approximately n=6-8/month in total).	(n<6 after the first month). If the recruitment rate falls behind, screening logs and reasons for exclusion will be explored after the first month to adjust eligibility criteria	No recruitment after two months
Completion of the outcome measures	Mean <120 minutes to complete all objective outcome measures and that at least 67% of patients found the duration acceptable	Between 121-150 minutes or only 50-66% of patients found the duration acceptable	>150 minutes or <50% of patients found the duration acceptable
Patient retention	10 or more patients show up at 16-week follow up	Only 6-9 patients show up at 16-week follow up	Below six patients show up at 16-week follow up
Adherence to exercise intervention	Minimum 75% of patients adhering to at least 75% of exercise sessions	Only 50-75% of patients adhering to 50-75% of exercise sessions	<50% of patients adhering to <50% of exercise sessions
Adverse events	No or minor adverse events with no patients discontinuing the study	Minor or serious adverse events leading to 2 or fewer patients discontinuing the study	Serious adverse events leading to >2 patients discontinuing the study

Research progression criteria were based on a traffic light system of green (go), amber (amend) and red (stop).[92] The research group evaluated the results of these research progression criteria and recommended whether to proceed with the definitive randomised controlled trial and which amendments needed to be made before proceeding, according to the prespecified criteria.

Definition of the primary outcome

Paper I-IV

The primary outcome (Paper II and IV) was self-reported shoulder pain, function and shoulder related quality of life, measured using the WOSI total score developed for patients with shoulder instability.[97] The WOSI has 21 questions, each marked on a scale from 0 to 100, with 0 being the best score (no limitations related to the shoulder) and 100 representing the worst score, with a total ranging from 0 to 2100 points.[98] It consists of four subscales: physical symptoms (10 questions; a maximum score of 1000); sports/recreation/work (4 questions; a maximum score of 400); lifestyle (4 questions; a maximum score of 400); and emotion (3 questions; a maximum score of 300). A Danish-validated digital version was used.[99]

For Paper I, the WOSI total was used as a secondary outcome since the research progression criteria were used as the primary outcomes. In Paper III, the WOSI was used as one of several self-reported characteristics at baseline.

Definition of self-reported mechanical shoulder symptoms

Paper III

Mechanical shoulder symptoms were used as an exposure in Paper III. All patients answered the following question related to the presence of mechanical shoulder symptoms at inclusion:

"Please indicate which shoulder complaints you have (you can tick off more than one):

a) Pain

b) Other symptoms (instability, subluxation, and/or laxity).

Patients only selecting "Pain" were considered to have no mechanical shoulder symptoms. Patients who selected "Other symptoms" with or without concurrent pain were considered to have mechanical shoulder symptoms. However, this term has not been used previously in the literature concerning the shoulder, but the question and definition of mechanical symptoms were adopted and modified from previous knee studies.[100, 101] Having self-reported mechanical symptoms is different from the objective clinical signs of shoulder instability, subluxation, or laxity. Therefore, mechanical shoulder symptoms were included as a supplemental characteristic.

Self-reported and objective outcomes

Paper I-IV

A range of secondary self-reported and objective clinical measures was included related to symptoms, function, and quality of life to be able to compare the findings with previous studies (Paper I and IV), to evaluate potential reasons for the treatment effectiveness (Paper IV), and to describe the clinical characteristics of the patients (Paper III) (Table 7). The Global Perceived Effect (GPE) was used on each of the four WOSI subdomains (physical symptoms, sports/recreation/work, lifestyle, and emotions) to measure the patients' self-reported impression of important health changes. Patients rated the importance of their experienced change on a 7-point Likert scale ranging from "worse, an important worsening" to "better, an important improvement".[102, 103]

Other outcomes

Self-efficacy, patient expectations of treatment effectiveness, the Patient Acceptable Symptom State (PASS), and treatment failure (TF) were collected as stated in the trial registration and presented elsewhere.

Overview of outcomes in the studies

There was a structured schedule of enrolment, interventions, assessments, and visits for patients in the clinical studies (Paper I-IV) (Table 8).

Table 7. The secondary self-reported and objective measures used in the clinical studies

Outcome	Scale	Content
WOSI total	Total score 0-2100 (better to worse)	Shoulder function
WOSI subdomain: physical symptoms	Score 0-1000	Physical symptoms + pain
WOSI subdomain: sport, recreation, work	Score 0-400	Sport, recreation, work
WOSI subdomain: lifestyle	Score 0-400	Lifestyle, social functioning
WOSI subdomain: emotions	Score 0-300	Emotional wellbeing
Numeric pain rating scale[104]	Total score 0-10 (worse to better)	Shoulder pain
Numeric symptom rating scale	Total score 0-10 (worse to better)	Complaints due to mechanical shoulder symptoms (instability, subluxation, laxity)
Patient-Specific Function Scale[105]	Total score 0-10 (worse to better)	Patient nominated activities.
Checklist Individual Strength[106]	Total score 8-56 (better to worse)	Chronic fatigue.
COOP/WONCA[107, 108]	Total score 6-30 (better to worse)	Functional health status.
Tampa Scale of Kinesiophobia[109]	Total score 11-44 (better to worse)	Fear of movement.
Global Perceived Effect[102, 103]	7-point scales ranging from "worse, an important worsening" to "better, an important improvement"	Impression of important health changes.
EQ-5D-3L and EQ-5D-5L[110, 111]	<0 to 1 (worse to better)	Health-related quality of life.
EQ-VAS[110, 111]	0-100 (worse to better)	Perceived health as of "today"
Shoulder range of motion in internal and external rotation with the shoulder at 90˚ abduction using a HALO digital goniometer (Halo Medical Devices, Subiaco, Australia).[112, 113]	˚	Active and passive range of motion
Shoulder flexion proprioception assessed using a HALO digital goniometer.[114, 115]	Error in ˚	Shoulder joint reposition sense (low-range and mid-range)
Maximum isometric voluntary contraction in shoulder scaption, internal rotation and external rotation using a handheld dynamometer (IsoForce Dynamometer EVO2; Medical Device Solution AG)[113, 116]	Nm/kg	Isometric shoulder torque strength
The anterior and posterior load and shift,[117] sulcus sign,[117] Gagey,[117] apprehension,[117] relocation,[117] release,[117] Rotés Qúerol,[16] shoulder rotation[20], and shoulder flexion[20] tests.	Positive/negative	Shoulder laxity, hypermobility and instability

Abbreviations: COOP/WONCA, Dartmouth Primary Care Cooperative Research Network/World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians; EQ-5D-3L, European Quality of life - Five Dimensions – Three Level; EQ-5D-5L, European Quality of life - Five Dimensions – Five Level; EQ-VAS, European Quality of life - Visual Analogue Scale; WOSI, Western Ontario Shoulder Instability Index.

Table 8. Outcomes in Paper I-IV, and schedule of enrolment, interventions, assessments, and visits for patients in the randomised controlled trial (Paper IV). This table is modified from Paper II

	Paper I	Paper III	STUDY PERIOD (Paper II and IV)				
			Pre-allocation		**Allocation**	**Post-allocation**	
			Enrolment	Baseline	Week 0	Week 16	Week 52
Timepoint			*-t*	t_0	0	t_1	t_2
ENROLMENT							
Eligibility screening	x	x	x				
Informed consent	x	x	x				
Allocation					x		
INTERVENTION							
Intervention	x				♦———	———	
Comparator							
ASSESSMENTS							
Initial questionnaire and demographics	x	x	x				
IPAQ short version	x		x				
Anthropometry	x	x		x		x	
End of treatment questionnaire						x	x
Primary outcome measure							
WOSI total, 0-2100	x	x		x		x	x
Secondary self-reported outcomes							
WOSI Physical symptoms, 0–1000	x			x		x	x
WOSI Sports/recreation/work, 0–400	x			x		x	x
WOSI Lifestyle, 0–400	x			x		x	x
WOSI Emotions, 0–300	x			x		x	x
Shoulder pain last seven days				x		x	x
Lowest, highest, average, 0-10	x	x		x		x	x
Shoulder symptoms last seven days				x		x	x
Lowest, highest, average, 0-10		x		x		x	x
Patient-Specific Functional Scale, 0-10		x		x		x	x
Checklist Individual Strength, 8-56	x	x		x		x	x
COOP/WONCA, 6-30	x	x		x		x	x
Tampa Scale of Kinesiophobia, 11-44	x	x		x		x	x
Global Perceived Effect, 1-7	x					x	x
EQ-5D-3L, <0-1	x						
EQ-5D-5L, <0-1		x		x		x	x
EQ-VAS, 0-100	x	x		x		x	x
Secondary objective outcomes							
Range of motion							
Internal rotation passive, ˚	x	x		x		x	
Internal rotation active, ˚	x	x		x		x	
External rotation passive, ˚	x	x		x		x	
External rotation active, ˚	x	x		x		x	
Isometric shoulder torque strength							
Scaption, Nm/kg	x	x		x		x	
Internal rotation, Nm/kg	x	x		x		x	
External rotation, Nm/kg	x	x		x		x	
Proprioception in flexion							
Low range, error (˚)	x	x		x		x	
Mid-range, error (˚)	x	x		x		x	
High range, error (˚)	x						
Shoulder instability and laxity tests	x			x		x	
Other outcome measures							
Patient expectations, 1-7			x				
Self-Efficacy Questionnaire, 0-60				x		x	x
PASS, yes/no						x	x
Treatment failure, yes/no						x	x

Abbreviations: COOP/WONCA, Dartmouth Primary Care Cooperative Research Network/World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians; EQ-5D-3L, European Quality of life - Five Dimensions – Three Level; EQ-5D-5L, European Quality of life – Five Dimensions – Five Level; EQ-VAS, European Quality of life - Visual analogue scale; IPAQ, International Physical Activity Questionnaire; PASS, Patient Acceptable Symptom State; WOSI, Western Ontario Shoulder Instability Index.

Timeline for each patient

Paper IV

For Paper IV, following inclusion and baseline testing, patients were randomised to receive either HEAVY or LIGHT (Figure 14). Patients were followed up at 16-weeks (primary endpoint), but the data collection for the 12-month follow-up is ongoing and will be reported elsewhere.

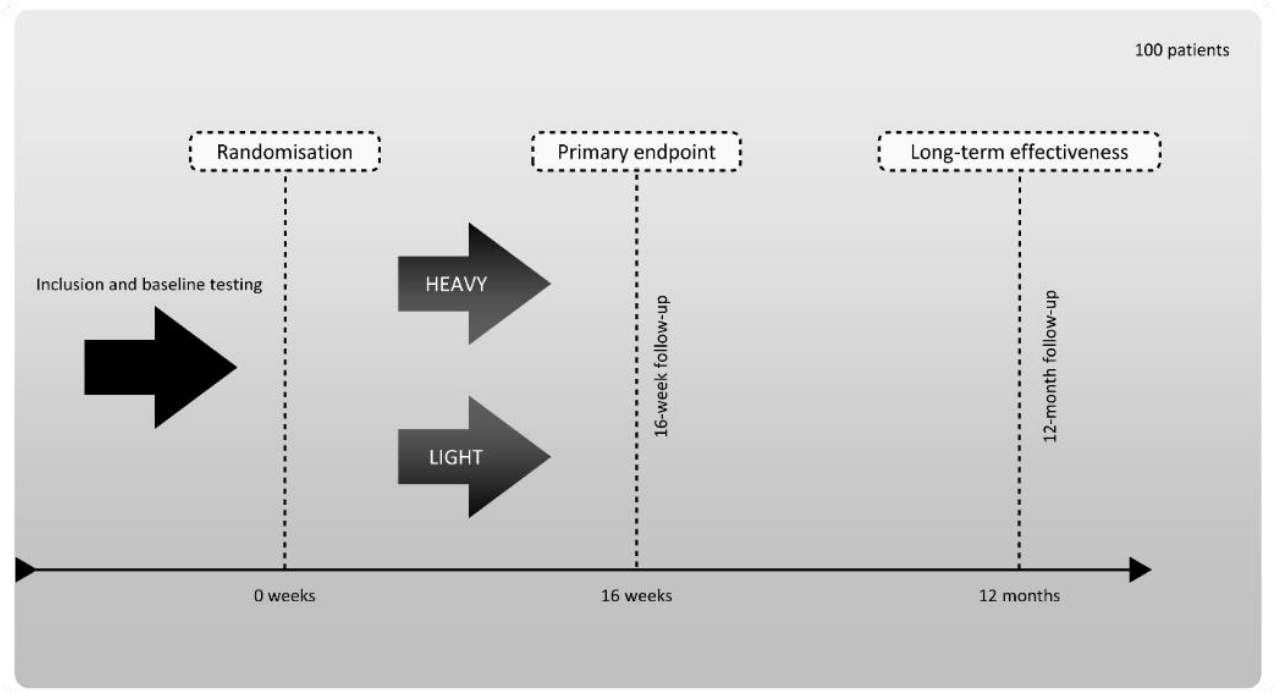

Figure 14. Timeline for each patient in the randomised controlled trial. Patients received either HEAVY (intervention) or LIGHT (comparator considered usual care in Denmark). The data collection for the 12-month follow-up is ongoing and will be reported elsewhere.

Randomisation and allocation concealment

Paper II, IV

The randomisation process is an essential part of a high-quality RCT study to reduce the systematic bias induced into the trial.[118] The randomisation eliminates selection bias by balancing both known and unknown predictors, and that any between-group difference at baseline reflects chance, so the groups are comparable. The allocation sequence, 1:1 using random block sizes, was computer-generated by a data manager outside the project, embedded digitally in the database of REDCap, and only available for the project manager who had no a priori knowledge of the next group assignment. Randomisation was performed after baseline tests.

Blinding

Paper II, IV

The principal investigator and the four outcome assessors were blinded from group allocation. The patients were kept blind to treatment allocation by being provided with minimal information about the content of the two exercise interventions and the study hypotheses. The patients were informed that the study compares two different exercise protocols using safe exercises to increase shoulder muscle function, and they were not told of the direction of our hypothesis. During the follow-up testing, patients were encouraged not to disclose or discuss what type of exercises they had performed with the outcome assessors. The treating physiotherapists were not blinded to group allocation since they were responsible for delivering both treatments. Blinding of the treating physiotherapists could have been achieved by separating clinics delivering the intervention (HEAVY) from clinics delivering the comparator (LIGHT), but this was deemed difficult for practical reasons. However, the treating physiotherapists were instructed to avoid talking to the patient about exercises in the opposite group and to ensure that patients from both groups were not in the clinic at the same time. The treating physiotherapists were blinded to testing results at baseline and follow-up. A biostatistician (EB) performed the analysis of the primary outcome in Paper IV blinded to group allocation. The principal investigator (BL) performed the secondary outcomes and per-protocol analyses blinded to group allocation.

Emergency unblinding was not relevant because the RCT includes two exercise-based interventions with strict load modification criteria related to the patients´ symptom response. Instead, in case of serious adverse events reported by patients or treating physiotherapists, patients would be referred to their general practitioner, as is the usual procedure in Denmark, and encouraged by the project manager to explain the type and intensity of exercises they had performed.

Sample size and power considerations

Paper I-IV

For Paper I, no sample size calculation was performed, but 12 patients were included based on the rationale for a feasibility study, regulatory considerations, and statistical considerations about a precise and representable mean and variance. [119]

For Paper II, a sample size calculation was performed to be used in the RCT (Paper IV). A mean baseline WOSI total of 1050 points was expected in patients with HSD/hEDS.[43, 120] The trial was powered to detect a between-group difference of at least 252 points on the WOSI total score,[98, 121] with a 350-point SD.[64, 120] This corresponded to an expected improvement of 48% in HEAVY (equal to 504 points with a baseline mean score of 1050 points) comparable with effects of previous interventions[63, 64, 67, 68, 120, 122] and 24%

improvement in LIGHT[63] (equal to 252 points with a baseline mean score of 1050 points). 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. With an expected dropout rate of 16%, 50 patients per group were enrolled in the RCT (Paper IV).[63, 64]

For Paper III, no power calculation was used because the study sample constituted baseline data from the RCT (Paper IV).

Statistics

Paper I-IV

For Paper I, research progression criteria were presented with descriptive statistics. Continuous data were assessed for normality (QQ-plots and histograms) and presented as mean ± standard deviation when fulfilling assumptions for normality, or as median [interquartile range] or proportion (%). Patient and physiotherapy feedback from questionnaires were reported descriptively and organised into categories related to recruitment procedures, assessment procedures, exercise intervention, intensity progression, adverse events, and perceived treatment effect for the individual patient. Changes from baseline to follow up on secondary outcomes were assessed using paired t-tests.

In Paper II, statistical analyses were planned (SAP published). The baseline characteristics were presented using descriptive analyses as mean, median, or proportion with 95% Confidence Interval (CI). Continuous data were checked for normality using the Shapiro-Wilk test and visual inspection of histogram and quantile-quantile plot. The primary analysis was performed at week 16 (primary endpoint). A multivariable linear regression model was used to assess the between-group difference at 16-weeks follow-up. The model included the primary outcome WOSI total at week 16 as the dependent variable and treatment group (HEAVY or LIGHT) as the main effect, adjusted for WOSI baseline score, age, sex, and the clustering around eight physiotherapy clinics (using cluster-robust standard errors). A similar approach was used for continuous secondary outcomes. For comparison of binary outcomes (clinical shoulder tests and GPE), multivariable logistic regressions were used to estimate the between-group odds ratio at 16-week follow-up, with the specific outcome as the dependent variable and treatment group as the main effect, adjusted for the baseline score of the outcome of interest, age, sex, and the clustering around physiotherapy clinics (using cluster-robust standard errors). For adverse events, self-reported pain medication use, and other concomitant treatments received, the crude difference between risks and medians were calculated with 95% CIs based on the "as observed" data while still respecting the original group allocation.

For Paper III, the demographic characteristics, medical history, and self-reported clinical and objective characteristics were presented using descriptive analyses as mean, median, or proportion with 95% CI. Continuous data were checked for normality using the Shapiro-Wilk test and visual inspection of histogram and quantile-quantile plot. To avoid multiple comparisons, no formal comparisons were made, but 95% CIs were used to describe group differences. The assumptions of the pre-registered and intended discriminant analyses were violated, so logistic regression analyses were used instead to study the association between group (presence of mechanical symptoms or not) as the categorical dependent variable, and the self-reported (model 1) and objectively measured (model 2) characteristics as the independent variables. Backwards stepping was conducted with p-values used to remove variables at a max set-point of 0.10. An additional analysis (model 3) using variables from the patients' medical history (Beighton score, symptom duration, previous shoulder dislocation, feel shoulder is loose, and have had previous shoulder treatment) and a model (model 4) combining all characteristics with $p < 0.1$ from the first three models were added. The model assumptions for the analyses were not violated since there was no multicollinearity among the independent variables (inspecting variance inflation factors <10) and no specification error (the logit of the outcome variable was a linear combination of the independent variables).

In Paper IV, the planned statistical analyses were performed as described in Paper II. The assumptions underlying the regression models were met. Multiple imputation was used for missing data at follow-up with age, sex, group allocation (masked), and baseline values as predictors. For sensitivity purposes, multiple imputation using baseline values carried forward was completed. Furthermore, a post hoc analysis of the number of successful (WOSI total score above 252 points) patients in HEAVY and LIGHT was performed.

All statistical analyses were performed using Stata (StataCorp. 2019. Stata Statistical Software: Release 16 and 16.1. College Station, TX: StataCorp LLC). The level of significance was set to 5% for all analyses.

Intention-To-Treat

Paper II, IV

In the primary analysis of the trial outcomes and the safety analysis (adverse events (AE)), all patients were included according to the treatment they originally were randomised to receive, following the Intention-To-Treat (ITT) principle. The distribution of the primary outcome (change score in WOSI total score) was visualised by dot plots and described by mean and 95% CI for each of the two groups (Paper IV).

Per protocol

Paper II, IV

The population was divided into two disjoint subpopulations concerning randomisation and treatment adherence. All patients were offered follow-up testing regardless of their exercise adherence during the 16-week intervention period.

In the spirit of a per-protocol analysis, the following formal comparison was performed:

Patients randomised to HEAVY who had good adherence and did not receive new, important interventions other than the assigned treatment in the follow-up period (e.g., surgery, steroid injection, or concomitant supervised exercise-based treatment for the shoulder)	vs	Patients randomised to LIGHT who had good adherence and did not receive new, important interventions other than the assigned treatment in the follow-up period (e.g., surgery, steroid injection, or concomitant supervised exercise-based treatment for the shoulder)

Covid-19 precautions

Paper II, IV

March 11, 2020, the Danish Government closed the physiotherapy clinics due to the Covid-19 pandemic. After 2-3 months, the clinics opened gradually. Therefore, a sensitivity analysis was performed to compare the baseline of patients recruited before March 11, 2020, with those after. Another sensitivity analysis was performed to compare the adherence of those who finished the intervention before March 11, 2020, with those later. Significant differences are reported.

Results

Feasibility of progressive high load strength training

Paper I

Twenty-two patients were assessed for eligibility from 25th April to 11th July 2018, and 12 patients (11 females) were included (Figure 15).

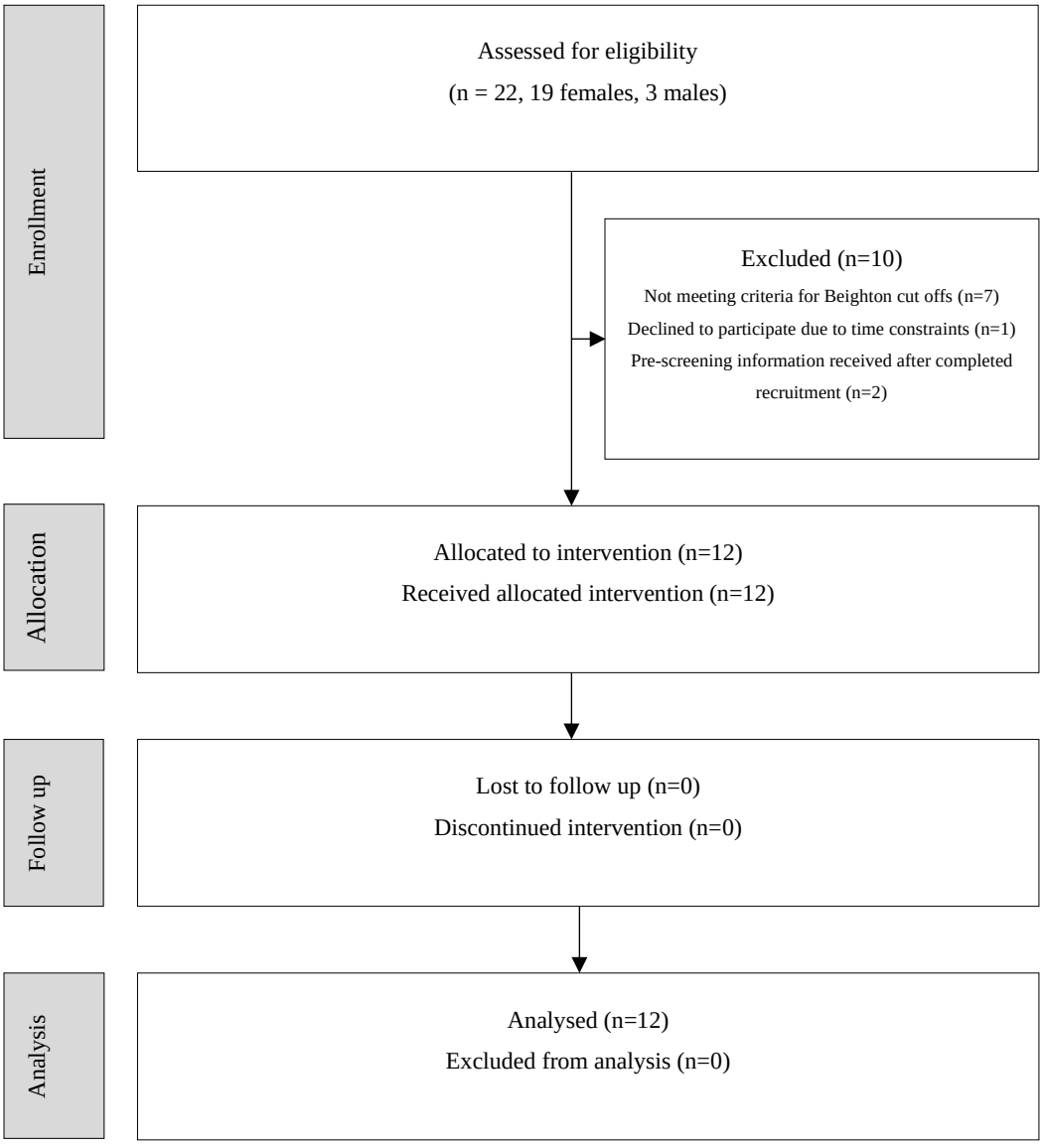

Figure 15. Flow diagram of patient enrolment, allocation, follow up, and analysis in Paper I. This figure is reused from Paper I.

Patients had a mean age of 39.3 (SD 13.9) and a median symptom duration of 36 (IQR 15-66) months (Figure 16). Eleven patients had shoulder pain at inclusion, while one did not experience pain but reported discomfort due to mechanical shoulder symptoms. The mean WOSI score at baseline was 1037 (SD: 215). Only one patient had previously received progressive high load strength training for the affected shoulder. All 12 patients received the exercise intervention and were included in the analysis.

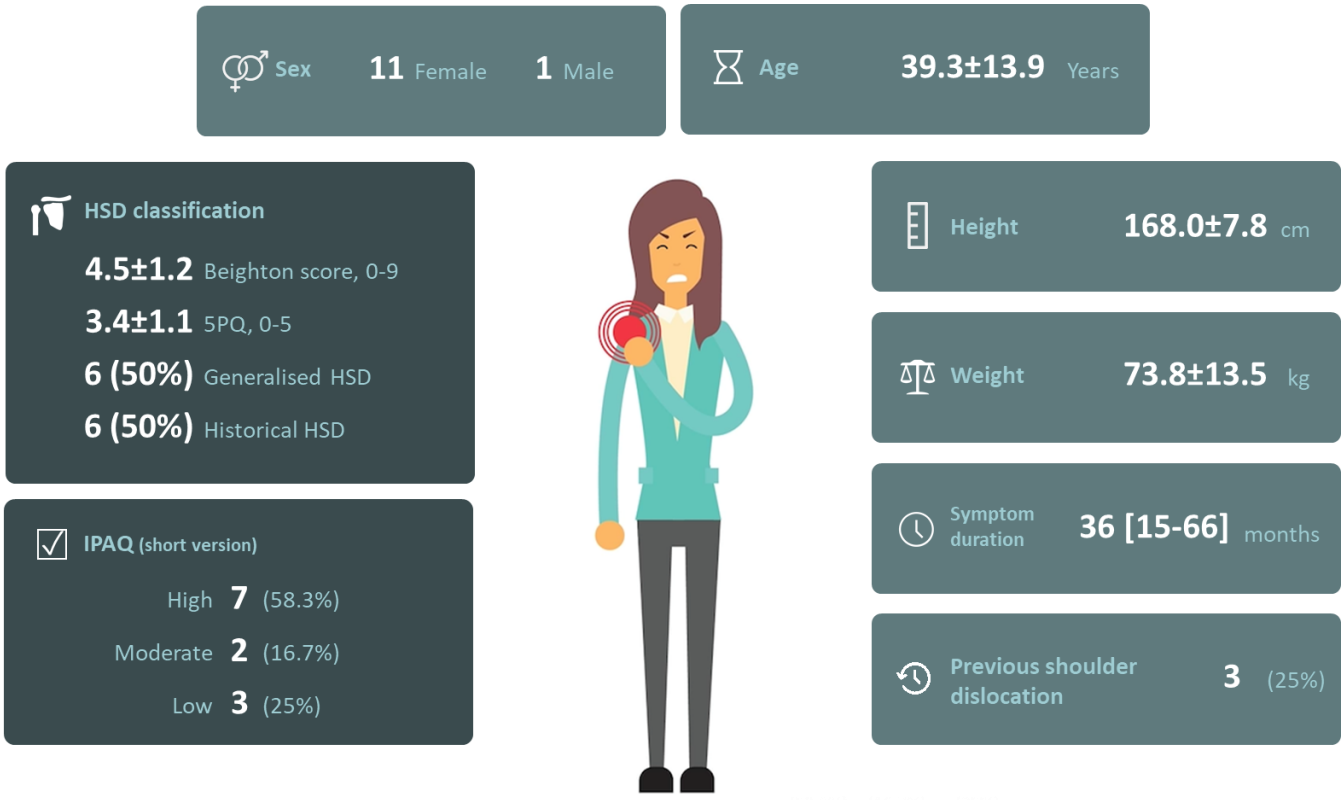

Figure 16. Baseline demographics for patients with hypermobility spectrum disorders (HSD) and persistent shoulder symptoms in the feasibility study (Paper I) (n = 12). Data are presented as mean ± standard deviation, median [interquartile range], or number (percentage). Abbreviations: 5PQ, Five-Part Questionnaire; IPAQ, International Physical Activity Questionnaire. Colourbox.dk / #89043.

Primary outcomes

Except for the recruitment rate at 5.6 patients/month, the level of acceptance was met for all other research progression criteria (assessment duration, patient retention, adherence, adverse events) (Figure 17). Four patients reported minor adverse events: transient soreness, shoulder ache, and `stuck´ shoulder (twice) (patient 5); headache

and general soreness after exercising (patient 7); acceptable soreness (patient 10); new pain sensation during handball throws (patient 12).

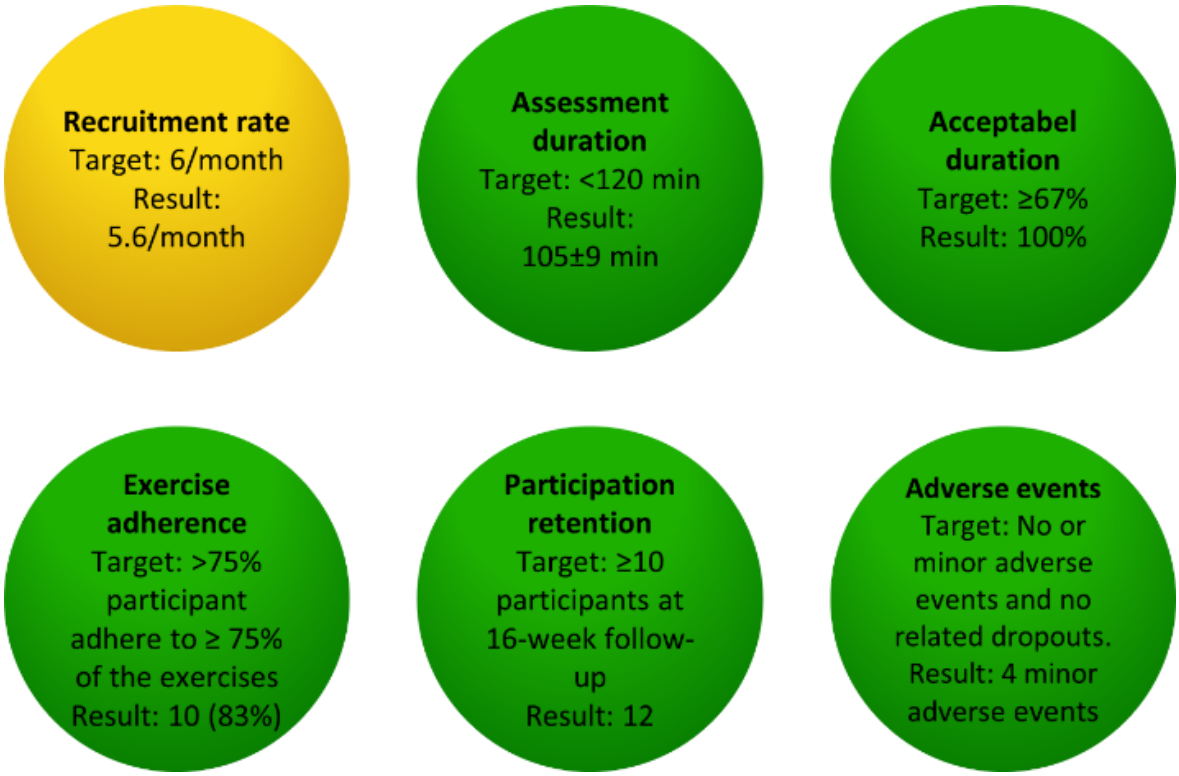

Figure 17. Primary outcomes in research progression criteria to inform the definitive randomised controlled trial. These research progression criteria were based on a traffic light system of green (go), amber (amend) and red (stop).[92]

Patient and physiotherapist feedback

Physiotherapists (100%) and patients (75%) were satisfied with the study design and intervention. Generally, the patients had not been offered progressive high load shoulder strength training for their shoulder complaints before their inclusion in this study. Although some patients found the exercise programme demanding, they found it relevant (Figure 18). The patients highlighted the importance of regular intensive supervision to ensure exercises were performed correctly and that exercise progression was adequately applied. The physiotherapists were satisfied with the 3-hour educational course about the intervention and found the exercise programme valuable with adequate descriptions of exercise progression criteria (p. 39). Four patients and all physiotherapists requested dumbbells that could be adjusted with lighter weights for precise exercise load progression (p. 39).

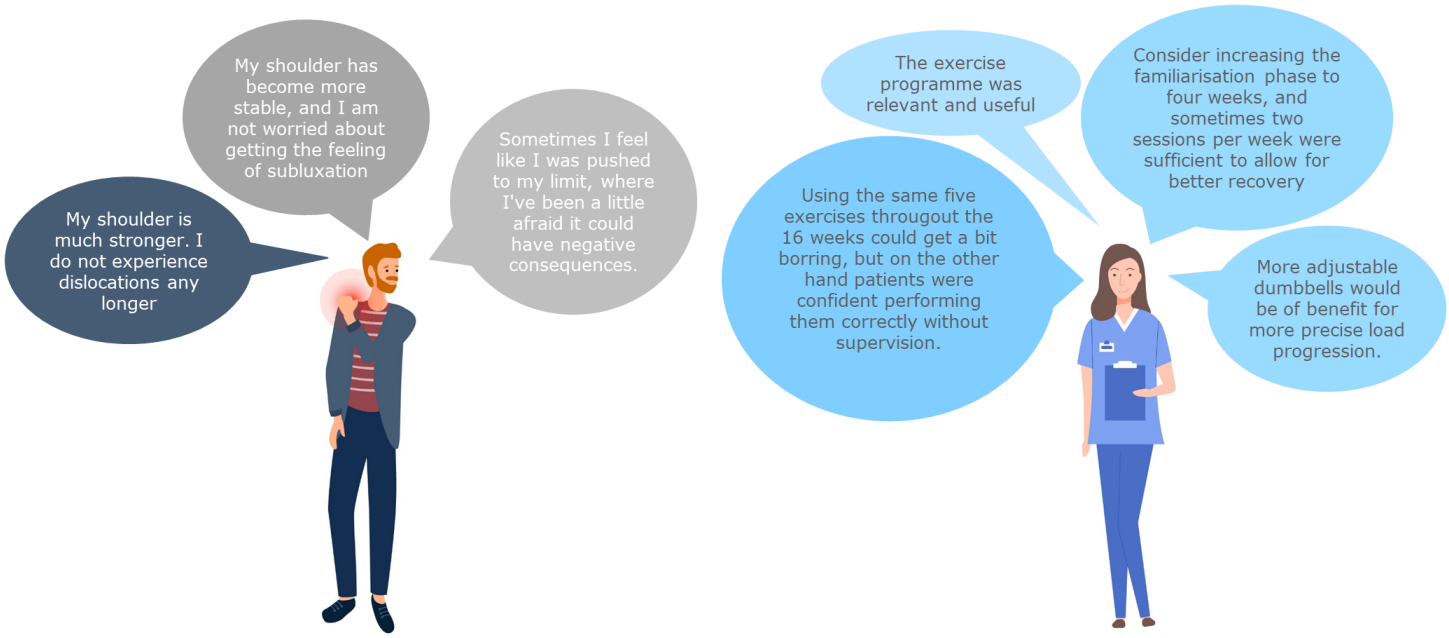

Figure 18. Patient and physiotherapist feedback on the progressive high load strengthening exercise programme from the feasibility study was useful to inform the randomised controlled trial. Colourbox.dk / robuart.

Secondary outcomes

All patients improved in WOSI total score (on average 51%) (Figure 19) and on all subscales. Patients reported less pain (46-69%), decreased kinesiophobia (13%) and lower levels of fatigue (23%), and 83% had positive scores on GPE (patients 3 and 7 had -1 and 0, respectively). Overall functional status (COOP/WONCA) and general health (EQ-5D-3L) improved by 8% and 1-10%, respectively. Patients improved in shoulder strength, and the clinical tests indicated decreased shoulder laxity/instability, thereby supporting the potential benefits of the intervention.

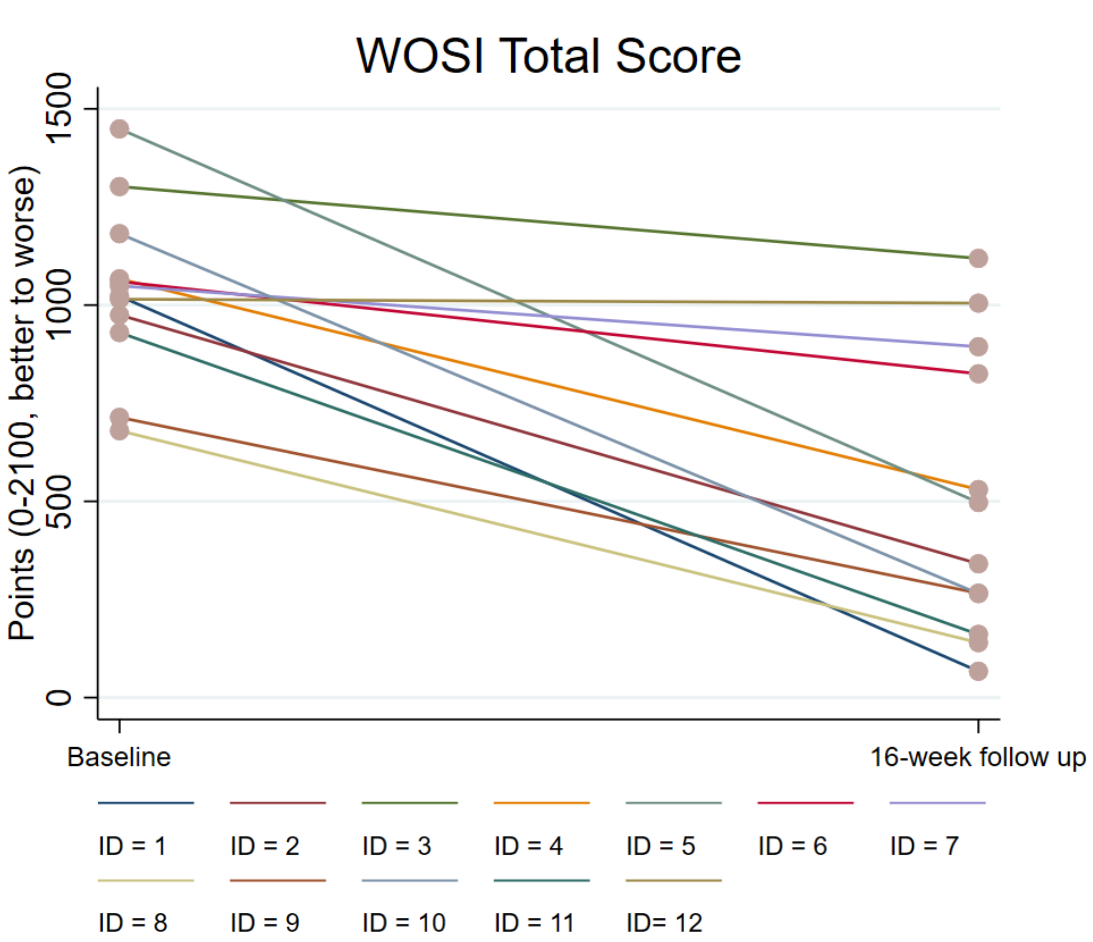

Figure 19. The Western Ontario Shoulder Instability Index (WOSI) total score for every patient from baseline to follow-up after 16 weeks of progressive high load shoulder strengthening exercise programme in Paper I. This figure is reused from Paper I.

Baseline clinical characteristics

Paper III

Of 100 included patients (79% females), 67% reported mechanical shoulder symptoms (61 patients with concurrent pain and six patients without pain) (Figure 20). Patients with mechanical symptoms were younger (means 35.1 vs 43.3), had longer symptom duration (median 46 vs 24 months), a larger proportion reported having had a previous shoulder dislocation (25% vs 3%), and a higher proportion of "feeling shoulder is loose" (64% vs 15%) (Figure 20, Figure 21). Further, a larger proportion of patients with mechanical symptoms had received prescriptions of analgesic medication (22 vs 12%) and other treatment modalities (steroid injection/surgery) (24 vs 15%).

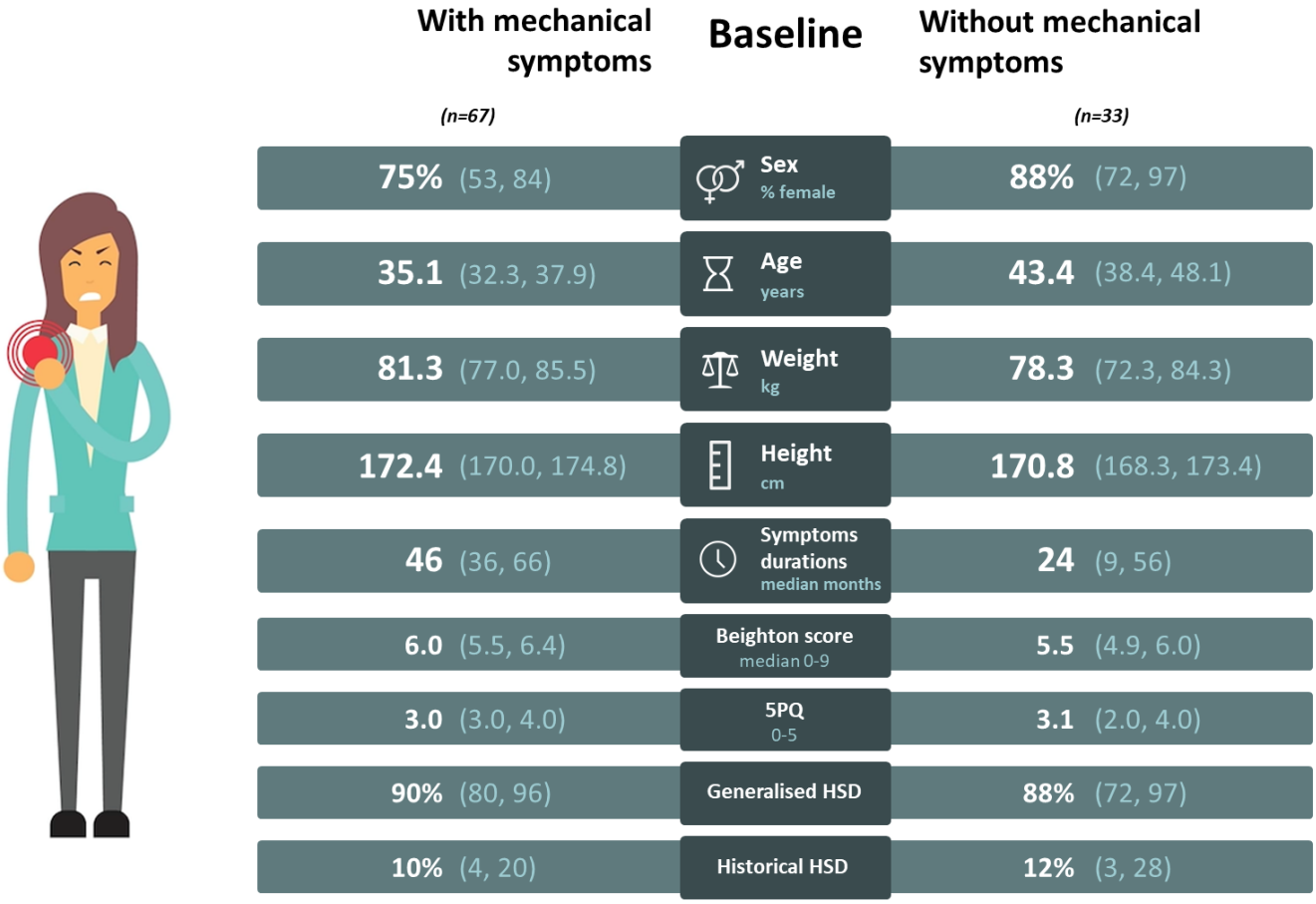

Figure 20. Demographics and self-reported medical history in patients with hypermobility spectrum disorders (HSD) and persistent shoulder complaints distributed by presence and absence of mechanical shoulder symptoms (instability, subluxation and/or laxity). Data are presented as mean, median, or proportion in % with 95% CI. Abbreviation: 5PQ, Five-Part Questionnaire. Colourbox.dk / #89043.

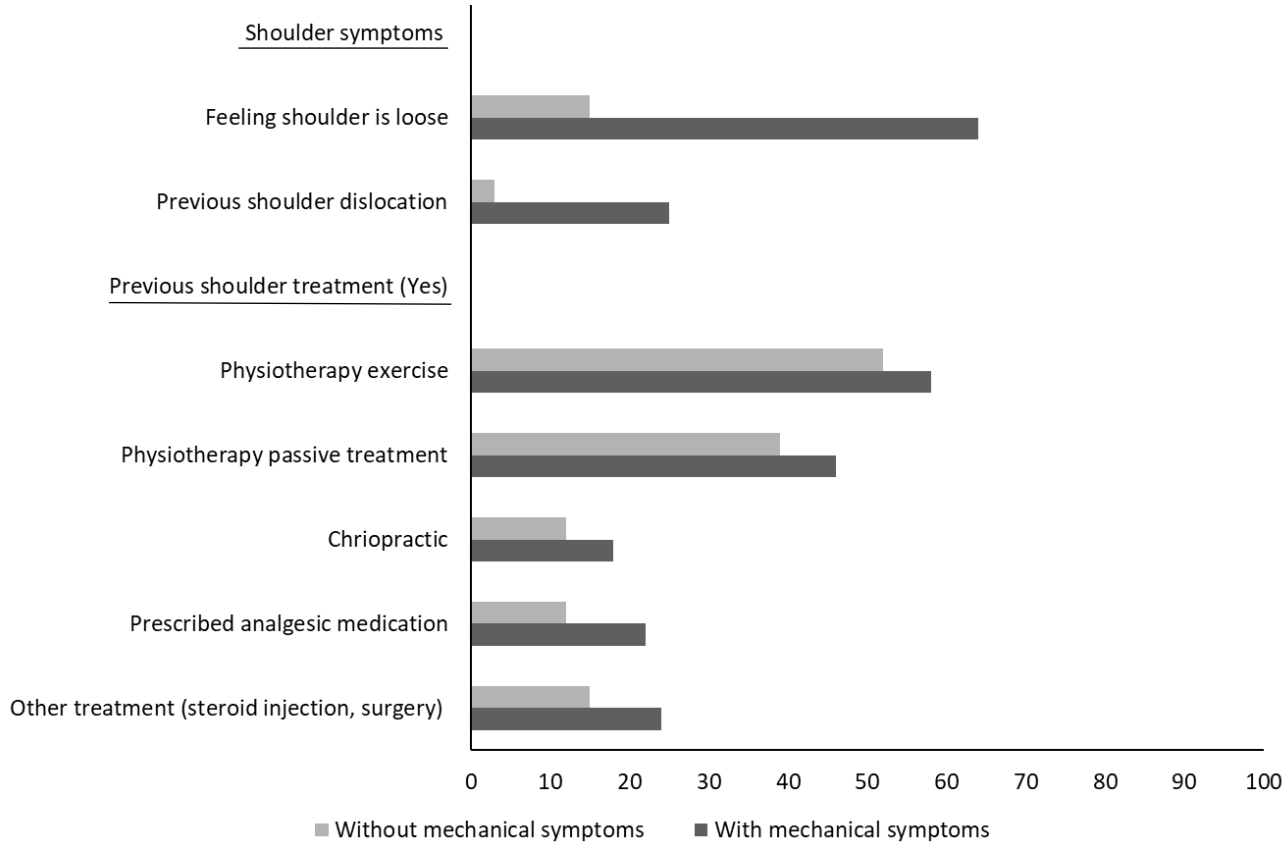

Figure 21. Self-reported medical history in patients with hypermobility spectrum disorders (HSD) and persistent shoulder complaints (proportion in %) distributed by presence and absence of mechanical shoulder symptoms (instability, subluxation and/or laxity).

The mean WOSI total score was 1056.8 (984.5; 1129.1) for all patients and higher in patients with mechanical shoulder symptoms (1088.2 vs 993.1) (Table 9). For each WOSI item, patients with mechanical symptoms scored at the same level or somewhat worse (Figure 22). However, items number 5 ("How much clicking, cracking, or snapping do you experience in your shoulder?") and 8 ("How much feeling of instability or looseness do you experience in your shoulder?"), which are directly related to experiencing mechanical symptoms showed the largest group differences.

Patients with mechanical symptoms reported higher levels of discomfort due to mechanical symptoms (means 4.0 (95% CI 3.5; 4.5) vs 2.4 (95% CI (1.7; 3.2)) and lower quality of life (means EQ-VAS 62.0 vs 70.0; and EQ-5D-5L index score 0.68 vs 0.73 (Table 9). Regarding CIS fatigue, a post hoc analysis showed that 61% in both groups had scores ≥ 35 points, considered to be severely fatigued (41/67 and 20/33 with and without mechanical symptoms, respectively). Regarding TSK-11, 49% of all patients had scores ≥ 24 points (37/67 and 12/33 with and without mechanical symptoms, respectively).

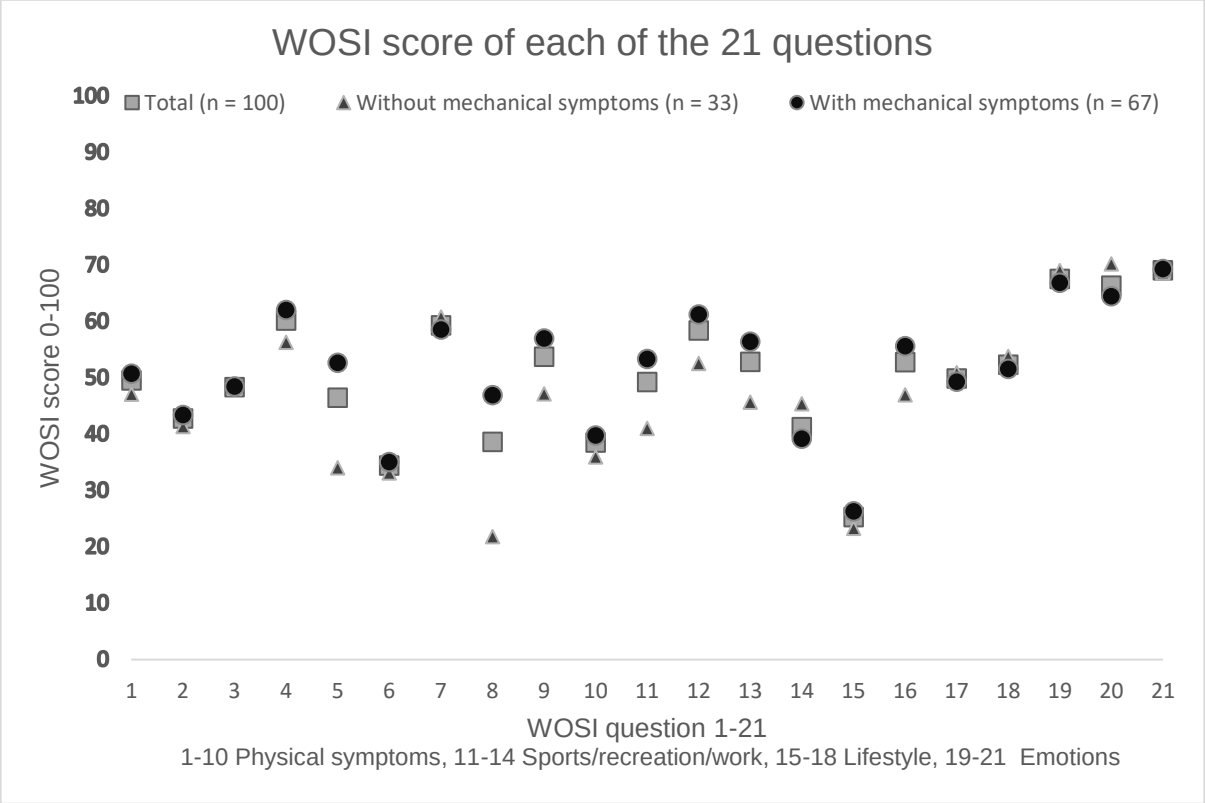

Figure 22. Mean score for each of the 21 Western Ontario Shoulder Instability Index (WOSI) questions (0-100, higher is worse) in patients with hypermobility spectrum disorders (HSD) and persistent shoulder complaints, presented for the entire group and distributed in groups by presence and absence of mechanical symptoms (i.e., instability, subluxation, and/or laxity). This figure is reused from Paper III.

Patients with mechanical symptoms were more likely to have additional discomfort due to mechanical symptoms (OR 1.48, 95% CI 1.17, 1.87) (model 1), a previous shoulder dislocation (OR 12.88, 95% CI 1.52, 109.03) (model 3), and to feel shoulder is loose (OR 10.88, 95% CI 3.59, 33.00) (model 3) (Table 10). The combined parsimonious model (model 4) was significant, with the same three variables remaining significant or marginally significant.

Table 9. Self-reported and objectively measured characteristics, including clinical tests in patients with hypermobility spectrum disorders (HSD) and persistent shoulder complaints presented for the entire group and distributed by presence and absence of self-reported mechanical shoulder symptoms (instability, subluxation and/or laxity). This table is reused from Paper III

Variables	All patients mean (95% CI) (n = 100)	Mechanical symptoms mean (95% C.I) (n = 67)	No mechanical symptoms mean (95% C.I) (n = 33)
Self-reported			
WOSI total score, 0-2100	1056.8 (984.5; 1129.1)	1088.2 (993.8; 1182.6)	993.1 (883.2; 1102.9)
Physical symptoms, 0-1000	471.9 (436.2; 507.6)	494.7 (448.5; 540.9)	425.6 (372.0; 479.3)
Sports/recreation/work, 0-400	201.7 (182.7; 220.8)	210.1 (186.6; 233.7)	184.6 (151.3; 217.9)
Lifestyle, 0-400	180.2 (163.4; 197.0)	182.8 (161.2; 204.4)	175.0 (147.6; 202.4)
Emotions, 0-300	203.0 (191.6; 214.3)	200.6 (185.5; 215.6)	207.8 (191.0; 224.7)
Shoulder pain intensity (NPRS) during the past seven days			
Lowest, 0-10	2.4 (2.0; 2.8)	2.3 (1.8; 2.8)	2.5 (1.9; 3.2)
Highest, 0-10	6.2 (5.7; 6.7)	6.5 (5.8; 7.1)	5.7 (5.0; 6.4)
Average, 0-10	4.0 (3.6; 4.4)	4.1 (3.5; 4.7)	3.7 (3.1; 4.3)
Discomfort due to mechanical shoulder symptoms (NRS) during the past seven days	2.5 (2.0; 2.9)	2.7 (2.1; 3.2)	2.0 (1.3; 2.7)
Lowest, 0-10	4.7 (4.1; 5.2)	5.3 (4.7; 5.8)	3.4 (2.5; 4.3)
Highest, 0-10	3.5 (3.0; 3.9)	4.0 (3.5; 4.5)	2.4 (1.7; 3.2)
Average, 0-10			
Tampa Scale of Kinesiophobia, 11-44	22.7 (21.6; 23.8)	23.3 (21.9; 24.6)	21.7 (19.7; 23.7)
CIS, fatigue subscale, 8-56	37.0 (34.9; 39.1)	37.4 (34.8; 39.9)	36.4 (32.4; 40.4)
COOP/WONCA, 6-30	14.4 (13.7; 15.2)	14.6 (13.7; 15.6)	14.1 (13.1; 15.1)
EQ-5D-5L, < 0-1	64.7 (60.7; 68.6)	62.0 (56.8; 67.2)	70.0 (64.5;75.6)
EQ-VAS, 0-100	0.69 (0.67; 0.72)	0.68 (0.64; 0.71)	0.73 (0.69; 0.77)
Objective			
Isometric shoulder torque strength, Nm/kg			
Scaption	0.45 (0.41; 0.49)	0.46 (0.41; 0.52)	0.42 (0.34; 0.49)
Internal rotation	0.33 (0.30; 0.36)	0.33 (0.30; 0.37)	0.32 (0.27; 0.38)
External rotation	0.24 (0.22: 0.26)	0.25 (0.23; 0.28)	0.23 (0.19; 0.27)
Range of motion, ˚			
Internal rotation passive	69 (66; 73)	68 (64; 73)	72 (65; 79)
Internal rotation active	67 (63; 70)	65 (61; 69)	70 (64; 77)
External rotation passive	103 (98; 107)	102 (96; 108)	104 (96; 112)
External rotation active	100 (95; 104)	100 (95; 105)	99 (91; 106)
Proprioception in flexion, error ˚			
Low range (55°±10°)	4.8 (4.2; 5.3)	4.7 (4.0; 5.4)	4.9 (3.8; 6.0)
Mid-range (90°±10°)	4.0 (3.6; 4.5)	4.1 (3.6; 4.7)	3.8 (3.0; 4.6)

Abbreviations: CIS, Checklist Individual Strength; 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 – Five Dimensions – Five Level; NPRS, Numeric Pain Rating Scale; NRS, Numeric Rating Scale; VAS, Visual Analogue Scale; WOSI, Western Ontario Shoulder Instability Index.

Table 10. Self-reported and objectively measured characteristics in patients with hypermobility spectrum disorders (HSD) and persistent shoulder complaints by presence and absence of self-reported mechanical shoulder symptoms (instability, subluxation and/or laxity). Results from logistic regression analyses using backwards stepping with p-values used to remove at a set-point of 0.10. This table is reused from Paper III

Variables	OR	95% CI	*p*-value
Model 1 - Self-reported characteristics			**<0.001***
Discomfort due to mechanical shoulder symptoms (mean past seven days), 0-10 NRS	1.48	1.17, 1.87	**0.001**
Model 2 – Objective characteristics			0.121*
Isometric shoulder torque strength, Nm/kg			
Scaption	8.85	0.77, 101.29	0.079
Range of motion, ˚			
External rotation passive	0.95	0.91, 1.00	**0.035**
External rotation active	1.04	1.00, 1.09	0.055
Model 3 – medical history			**<0.001***
A previous shoulder dislocation (yes)	12.88	1.52, 109.03	**0.019**
Feeling shoulder is loose (yes)	10.88	3.59, 33.00	**<0.001**
Combined model			**<0.001***
Discomfort due to mechanical shoulder symptoms mean past seven days), 0-10 NRS	1.28	0.97, 1.68	0.079
A previous shoulder dislocation (yes)	10.88	1.25, 95.08	**0.031**
Feeling shoulder is loose (yes)	8.45	2.70, 26.43	**<0.001**

Abbreviation: NRS, Numeric Rating Scale.
P-values <0.05 are in bold.
*P-value for model.

Effectiveness of progressive high load strength training

Paper II, IV

Development of RCT protocol

A protocol for a high-quality RCT was designed and described following best practice recommendations from the initial trial registration and ethical approvement to publishing the protocol paper in an open-access journal.

Participants

Recruitment ran from March 2019, and the final 16-week follow-up was completed in February 2021 (patient flow through the trial in Figure 24). Of the 100 patients who were randomly assigned, 93 patients (93%) were followed up postintervention. Patients were mainly females (79%), had a mean age of 37.8 years (Figure 23). In total, 54 patients fulfilled the criteria for a diagnosis of anterior shoulder instability, 78 patients for multidirectional instability, and 90 patients had at least one positive shoulder hypermobility test, while four patients could not be placed in these groups. A total of 67 patients adhered to the interventions and constituted the per-protocol population.

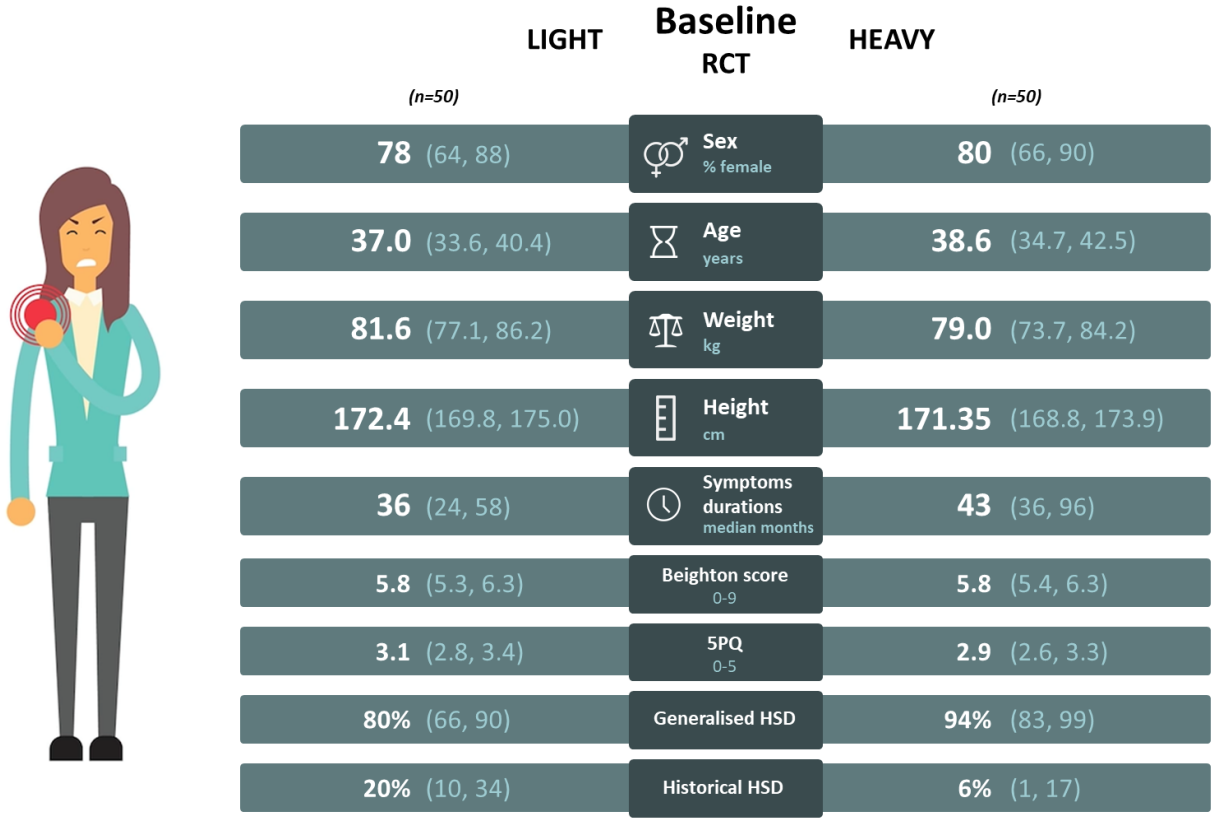

Figure 23. Baseline characteristics for patients in HEAVY and LIGHT. Continuous data are presented as mean or median with 95% confidence interval (CI), and categorical variables are presented as proportion % (95% CI). Abbreviations: HSD, Hypermobility Spectrum Disorders; 5PQ, Five-Part Questionnaire. Colourbox.dk / #89043.

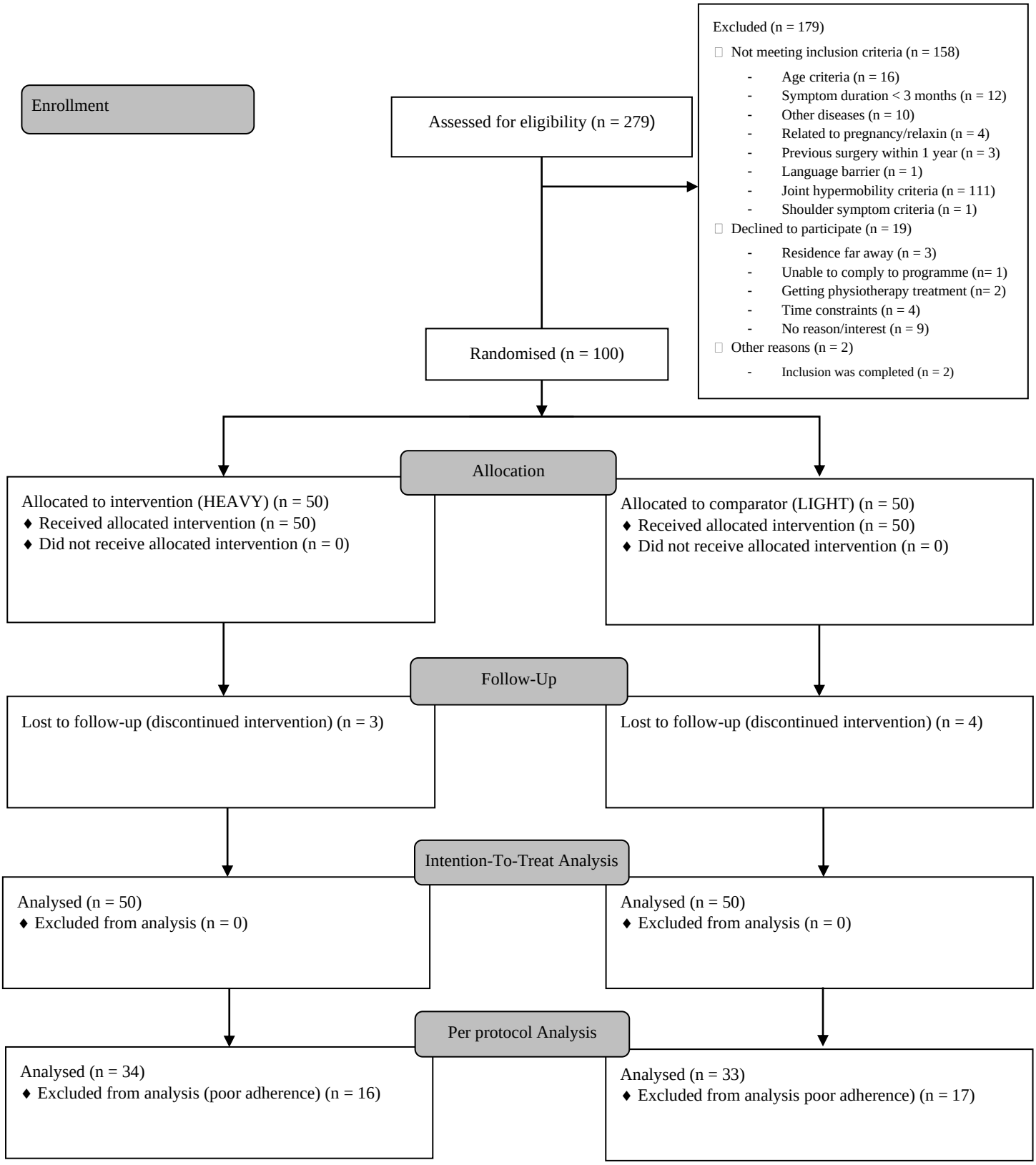

Figure 24. CONSORT participant flow chart. This figure is reused from Paper IV.

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 11, Figure 25). 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, 11.9%). The sensitivity analysis supported these findings (data not shown). The proportion of successful patients favoured HEAVY (ITT 68% vs 54%, per protocol 85% vs 55%).

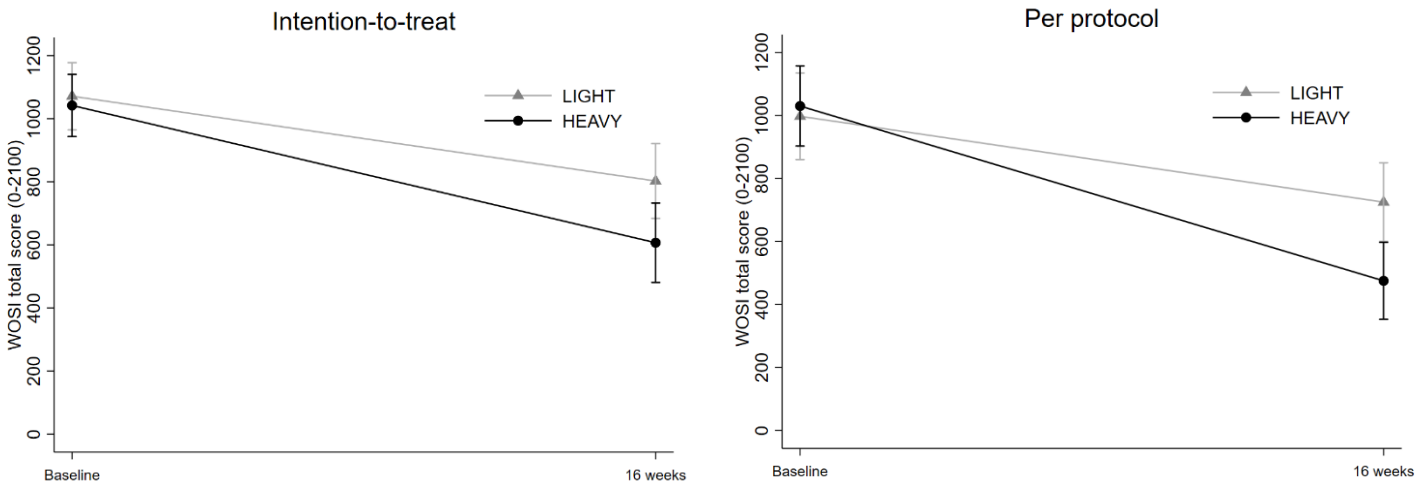

Figure 25. *The primary outcome at 16-week follow-up for HEAVY and LIGHT in patients with hypermobility spectrum disorders (HSD) and persistent shoulder complaints. Intention-To-Treat (n = 100), per protocol (n = 67).*

Secondary outcomes

The secondary outcomes favoured HEAVY, but most were non-significant. 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, 5.24). There were no serious adverse events, but HEAVY reported significantly more transient muscle soreness and headaches (Table 12). Two patients from HEAVY dropped out due to adverse events. There were no differences between the use of painkillers and concomitant treatment between the groups at baseline and postintervention (Appendix VII).

Impact of the Covid-19 pandemic

The Covid-19 pandemic did not significantly impact the patients' baseline level of shoulder function (WOSI) or adherence. Still, the patients did not have access to face-to-face supervision during the 2-3 months' lockdown of physiotherapy clinics. Some clinics provided teleconsultation using the phone and video.

Table 11. Outcomes at 16-week follow-up for HEAVY and LIGHT. This table is reused from Paper IV

	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, 921.3)	606.9 (481.1, 732.7)	**-195.7 (-367.7, -23.7)**	**-174.5 (-341.4, -7.7)**
Secondary self-reported outcomes					
WOSI Physical symptoms (scale 0–1000)	96/97	346.5 (286.9, 406.2)	279.0 (222.4, 335.6)	-67.5 (-149.3, 14.3)	-68.6 (-144.7, 7.4)
WOSI Sports/recreation/work (scale 0–400)	96/97	150.7 (121.6, 179.9)	111.8 (82.4, 141.2)	-38.9 (-79.4, 1.6)	-30.7 (-70.6, 9.2)
WOSI Lifestyle (scale 0–400)	96/97	134.5 (108.3, 160.8)	96.6 (70.1, 123.0)	-38.0 (-75.0, -1.1)	-31.2 (-63.1, 0.8)
WOSI Emotions (scale 0–300)	96/97	169.3 (147.9, 190.8)	121.7 (98.8, 144.6)	**-47.6 (-78.9, -16.4)**	**-43.5 (-72.0, -14.9)**
Shoulder pain last seven days (scale 0-10)					
Lowest rating	95/97	1.3 (0.7, 1.9)	1.1 (0.6, 1.6)	-0.2 (-1.0, 0.5)	-0.3 (-1.0, 0.4)
Highest rating	95/97	4.0 (3.2, 4.8)	2.8 (2.1, 3.5)	**-1.2 (-2.2, -0.1)**	-1.0 (-2.0, 0.1)
Average rating	95/97	2.3 (1.6, 2.9)	1.7 (1.1, 2.3)	-0.6 (-1.4, 0.3)	-0.5 (-1.5, 0.5)
Discomfort due to mechanical symptoms last seven days (scale 0-10)					
Lowest rating	95/97	1.3 (0.8, 1.7)	1.1 (0.6, 1.6)	-0.1 (-0.8, 0.5)	-0.2 (-0.9, 0.5)
Highest rating	95/97	3.0 (2.3, 3.7)	2.2 (1.6, 2.8)	-0.8 (-1.7, 0.1)	-0.6 (-1.2, 0.1)
Average rating	95/97	1.9 (1.4, 2.5)	1.5 (1.0, 2.1)	-0.4 (-1.1, 0.3)	-0.2 (-0.9, 0.4)
Patient-Specific Functional Scale (scale 0-10)	95/97	5.6 (4.8, 6.3)	5.7 (5.0, 6.5)	0.2 (-0.9, 1.3)	0.2 (-1.0, 1.4)
Checklist Individual Strength (scale 8-56)	95/97	32.5 (28.7, 36.3)	29.8 (26.4, 33.1)	-2.7 (-7.7, 2.3)	-2.5 (-7.1, 2.2)
COOP/WONCA (scale 6-30)	94/97	14.0 (12.7, 15.3)	12.9 (11.6, 14.1)	-1.2 (-3.0, 0.6)	-0.5 (-2.2, 1.2)
Tampa Scale of Kinesiophobia, (scale 11-44)	94/97	22.2 (20.4, 24.1)	20.5 (18.8, 22.1)	-1.8 (-4.2, 0.7)	-0.8 (-2.7, 1.1)
EQ-5D-5L, (scale <0-1)	94/97	0.76 (0.72, 0.79)	0.80 (0.76, 0.83)	0.04 (-0.01, 0.09)	0.02 (-0.02, 0.07)
EQ-VAS (scale 0-100)	94/97	69.6 (64.0, 75.2)	75.3 (70.6, 80.1)	5.7 (-1.5, 13.0)	0.3 (-8.0, 8.6)

(*continued on next page*)

Table 11. (*Continued*)

Secondary objective outcomes					
Range of motion (˚)					
Internal rotation passive	87/90	72.6 (67.3, 78.0)	69.9 (64.7, 75.2)	-2.70 (-10.6, 5.2)	-0.6 (-11.3, 10.2)
Internal rotation active	87/90	68.9 (64.1, 73.7)	71.2 (66.8, 75.7)	2.4 (-4.5, 9.2)	4.0 (-4.2, 12.2)
External rotation passive	87/90	105.3 (96.9, 113.7)	107.6 (100.0, 115.1)	2.2 (-9.8, 14.3)	-0.5 (-16.4, 15.4)
External rotation active	87/90	100.6 (93.2, 108.1)	107.0 (100.5, 113.6)	6.4 (-4.2, 17.0)	3.4 (-10.8, 17.5)
Isometric shoulder torque strength (Nm/kg)					
Scaption	87/90	0.48 (0.42, 0.54)	0.52 (0.45, 0.59)	0.04 (-0.05, 0.14)	0.05 (-0.04, 0.13)
Internal rotation	87/90	0.37 (0.32, 0.42)	0.36 (0.30, 0.41)	-0.01 (-0.09, 0.06)	0.00 (-0.07, 0.07)
External rotation	87/90	0.25 (0.22, 0.28)	0.27 (.23, 0.31)	0.02 (-0.03, 0.07)	0.03 (-0.03, 0.08)
Proprioception in flexion (error ˚)					
Low range	87/90	4.65 (3.71, 5.60)	4.98 (3.85, 6.11)	0.33 (-1.24, 1.90)	0.65 (-1.60, 2.90)
Mid-range	86/90	3.34 (2.65, 4.04)	4.51 (3.47, 5.54)	**1.17 (0.01, 2.32)**	1.17 (-0.27. 2.60)
Shoulder instability and laxity tests (positive %) §					
Shoulder flexion test, positive = yes	87/90	78 (64, 91)	62 (47, 76)	OR 0.46 (0.17, 1.21)	OR 0.40 (0.09, 1.75)
Shoulder rotation test, positive >180˚	87/90	62 (47, 76)	42 (28, 56)	OR 0.44 (0.19, 1.03)	**OR 0.32 (0.13, 0.80)**
Apprehension test, positive = yes	87/90	70 (55, 85)	62 (48, 76)	OR 0.70 (0.29, 1.65)	OR 0.59 (0.31, 1.13)
Relocation test‖, positive = yes	87/90	55 (38, 72)	44 (30, 58)	OR 0.66 (0.28, 1.56)	OR 0.59 (0.33, 1.08)
Release test‖, positive = yes	87/90	50 (32, 68)	37 (23, 51)	OR 0.58 (0.24, 1.39)	OR 0.58 (0.25, 1.35)
Load and shift anterior, positive 2-3	87/90	68 (52, 84)	62 (47, 77)	OR 0.77 (0.31, 1.90)	OR 0.56 (0.23, 1.40)
Load and shift posterior, positive 2-3	87/90	28 (13, 44)	18 (7, 29)	OR 0.57 (0.20, 1.61)	OR 0.63 (0.19, 2.04)
Sulcus sign, positive >1 cm	87/90	84 (68, 93)	85 (70, 93)	OR 0.97 (0.28, 3.34)	OR 1.05 (0.28, 3.94)
Gagey, positive >105˚	87/90	92 (85, 100)	90 (78, 100)	OR 0.73 (0.15, 3.43)	OR 0.43 (0.14, 1.37)
Rotés Queról, positive > 90˚	87/90	63 (48, 77)	55 (41, 69)	OR 0.73 (0.31, 1.72)	OR 0.72 (0.20, 2.66)
Global Perceived Effect ‡ §					
(% rated important effect postintervention)					
Physical symptoms	45/47	44 (31, 59)	64 (49, 76)	OR 2.21 (0.96, 5.09)	**OR 2.37 (1.07, 5.24)**
Sports/recreation/work	45/47	38 (25, 53)	51 (37, 65)	OR 1.72 (0.75, 3.94)	OR 1.82 (0.82, 4.03)
Lifestyle	45/47	44 (31, 59)	55 (41, 69)	OR 1.55 (0.68, 3.52)	OR 1.60 (0.65, 3.96)
Emotions	45/47	40 (27, 55)	51 (37, 65)	OR 1.57 (0.69, 3.58)	OR 1.57 (0.51, 4.85)

* 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 WOSI score, age, sex, and the clustering around physiotherapy clinics.
‡ No data imputation
§ Proportions of a positive test in % (95% CI) and odds ratio (OR) for between-group differences with group LIGHT as reference.
‖ Relocation and release tests were only performed on patients with a positive apprehension test.
Abbreviations: CI, Confidence Interval; CIS, Checklist Individual Strength; 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 – Five Dimensions – Five Level; NPRS, Numeric Pain Rating Scale; OR, Odds Ratio; VAS, Visual Analogue Scale; WOSI, Western Ontario Shoulder Instability Index. Statistically significant results ($p<0.05$) are marked in bold.

Table 12. Adverse Events (specific, serious or minor, and withdrawals due to adverse events), and crude differences between risks were calculated with 95% Confidence Intervals based on the "as observed" data while still respecting the original group allocation, from baseline to 16-week follow-up for HEAVY vs LIGHT in patients with hypermobility spectrum disorder (HSD) and shoulder complaints. This table is modified from Paper IV

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

This table includes all adverse events that occurred during the 16-week study period but did not necessarily have a causal relationship with the treatment administered.
* Serious adverse events were unexpected but covered death, life-threatening events, disability, and permanent damage.
† One dropout was due to worsening of symptoms caused by lack of supervision during the Covid-19 pandemic lockdown, and one patient had suffered from a hand fracture not related to the intervention (data not included in this table).

Discussion

Summary of main findings

Paper I

The 16-week progressive high load shoulder strengthening exercise programme (HEAVY) was feasible in patients with HSD and persistent shoulder complaints regarding assessment duration, retention, adherence, and with few minor adverse events. Patient feedback was positive, and physiotherapists found the intervention relevant and applicable to the patient group. Therefore, an RCT could be successfully planned and initiated with an improved recruitment strategy.

Paper II

A superiority, parallel-group, randomised trial (1:1 allocation ratio, electronic concealment, random block sizes) was designed, with a required sample size of 100 patients. Patients would be allocated to receive progressive HEAVY (full range of motion, progressive high load) or low load strengthening exercises (LIGHT) (usual care, neutral to midrange of motion) three times weekly with exercises targeting scapular and rotator cuff muscles. The primary endpoint was defined as the between-group difference at 16-week follow-up in the primary outcome Western Ontario Shoulder Instability Index (WOSI, 0-2100 better to worse), and a wide range of secondary outcomes that could potentially support and explain any reported benefits of the intervention.

Paper III

All patients had substantial impairments related to shoulder pain, function, fatigue, fear of movement, and quality of life at baseline. Two-thirds of the patients reported mechanical symptoms. These patients were younger and more severely impaired than those without mechanical symptoms: a higher proportion reported longer symptom duration, previous shoulder dislocations, feeling the shoulder is loose, an increased odds of reporting additional discomfort, and having had received treatment.

Paper IV

At 16-week follow-up, HEAVY was statistically superior to LIGHT in self-reported shoulder function. Patients in HEAVY were less likely to have a positive shoulder rotation >180° and more likely to rate an important improvement in "physical symptoms" (GPE). There were no serious adverse events, but more patients undergoing HEAVY experienced transient muscle soreness and headaches.

Explanation of results and comparison with previous findings

Feasibility of using progressive high load strength training

Paper I

A feasibility study tries to answer the question "Can this study be done?" with the overarching aim of reducing the burden of research waste.[123, 124] The research progression criteria to inform the future RCT were based on recommendations for designing high-quality feasibility studies, focusing on assessing feasibility rather than effectiveness.[125] The most important research progression criteria cover recruitment rate, intervention adherence, and monitoring the completeness and quality of outcome data, all of which were included in the feasibility study.[92] As part of the intervention adherence, adverse events were monitored due to the nature of the intervention, including progressive high load shoulder strength training. This was done because this intervention has not previously been investigated in patients with HSD/hEDS, and the potential for non-adherence was high. Patient retention was also evaluated in the feasibility study, but this introduces the possibility for overestimating target retention rates in the main trial.[92]

The overall positive outcomes in the research progression criteria were ascribed specifically to the possibility for the patients to receive regular supervision (i.e., planned to be twice a week) during the 16-week intervention period, where the treating physiotherapist could motivate the patient to continue exercising and support in managing transient adverse events by both reassuring the patient and modifying the exercise intensity as needed. Since the supervision was an essential part of the intervention delivery, it was highly informative that the physiotherapist found the exercise leaflets and load progression criteria easy to follow and that both patients and physiotherapists in agreement experienced the exercise protocol as relevant and applicable to reduce shoulder complaints for this patient group in a primary care setting.

The feasibility study provided useful knowledge about the chosen secondary self-reported and objective outcomes, mainly confirming that the specific and generic outcomes were relevant. Since one patient did not have shoulder pain, and patients presented with impairments in many different daily activities, the feasibility study helped identify the relevance of extending the numeric pain rating scale to include a numeric rating scale related to complaints other than pain, i.e. due to mechanical shoulder symptoms (i.e., instability, subluxation and laxity), and that adding the Patient-Specific Functional Scale which includes the rating of self-nominated activities would be useful to support the generic outcomes.[105] Furthermore, the patients with symptoms above 90° of shoulder flexion had difficulties performing the proprioception

test at high range[114], which is why this test was removed during the protocol development (Paper II) for the RCT (Paper IV).

The feasibility study provided sufficient methodological evidence about the design, planning, and justification of a definitive RCT based on the research progression criteria, secondary outcomes, and qualitative feedback. However, an improved recruitment strategy was required since the criterion for recruitment rate was not *green*. The number of general practitioners and physiotherapy clinics in the recruitment process was increased to boost the recruitment rate. The inclusion of 100 patients could be expected to be feasible within two years.

Development of a high-quality randomised controlled trial

Paper II

The RCT was designed to address an important and severe condition using transparent, detailed, and high-quality methods to support future implementation. Initially, the primary investigator planned to perform all baseline and follow-up assessments. However, to reduce the risk of bias, a decision was made following the feasibility study to include blinded external physiotherapists not otherwise involved in the project to complete all baseline and follow-up assessments. This decision required several meetings, applying for further funding to pay the external physiotherapists, and providing educational sessions to align and standardise the testing procedures. Furthermore, a large effort was made to ensure that the same physiotherapist tested the same patient at both time points to ensure the test-retest reliability.

The intervention (HEAVY) developed for the feasibility study was kept without any changes to the protocol, besides creating the 3D-printed adjustable dumbbells to allow smaller intervals in load progression. Some important features of the intervention were the 3-week familiarisation based on a calculated 10 RM, the progressive increase in load and intensity, and the load progression criteria based on both self-reported (e.g., acceptable symptoms) and objectively measured (e.g., stable scapula during movement) quality in each exercise. The rationale for applying progressive high load strength training in this patient group was to impact the cross-sectional areas of the muscles, the voluntary activation of the available muscle mass, and potentially increase tendon stiffness. These changes were anticipated in a 16 weeks' perspective to increase the possibility to establish active support of the shoulder to compensate for the lack of passive stability.

An important reason for using an active comparator (LIGHT) was because the included patients had sought medical help by their own initiative. As such, it would have been considered unethical to offer them a placebo or no treatment (e.g., wait and see). To adhere to best practice guidelines during the planning of the RCT, an active exercise-based treatment was offered. Offering a placebo or no treatment could be a potential

barrier to study participation because patients could perceive the possibility of being allocated a placebo-only or no treatment as less desirable than the intervention.[126] The LIGHT programme was designed based on the clinical recommendations at that time for patients with HSD/HEDS, typically to consult a physiotherapist who could prescribe low load exercises, educate about the HSD/HEDS condition, and give advice on how to protect the joints in daily activities.[58, 59, 78] A common exercise application among researchers and clinicians was introducing scapula and posture corrective exercises. Then closed kinetic chain exercises would be performed in neutral to mid-range positions and with no load or limited external loads applied to avoid excessive shear stress on the joint before introducing more functional and full range open kinetic chain movements. Another benefit of comparing the intervention with another exercise-based treatment inspired by previous exercise programmes[63, 64, 79] instead of placebo or no treatment was that it would lessen the likelihood of overestimating the treatment effectiveness.

The severity of shoulder impairments

Paper III

A high mean WOSI total score (1056.8, 95% CI 984.5, 1129.1) was reported for both groups at baseline. This score is substantially larger than scores reported in individuals with healthy shoulders (84/2100 points[127]) and comparable to functional shoulder impairments in patients with HSD and shoulder complaints[120], hEDS[43], MDI[64], and following traumatic shoulder dislocation[63], emphasising the severity of the symptoms.

The shoulder pain intensities (NPRS) (for all patients lowest mean 2.4, highest mean 6.2) were similar between groups yet comparable with pain intensities commonly reported for subacromial pain syndrome (or rotator cuff related shoulder pain) varying between 2.4/2.8 and 5.7/6.3, depending on pain definitions[128] – representing a patient group responsible for 45-80% of all shoulder related contact in general practice.[129, 130]

Previous studies on hEDS show that moderate to severe pain, besides being prevalent in their daily life, is related to dislocations, hypermobility, and previous surgery.[41, 131] Furthermore, patients with severe fatigue report higher pain intensities than patients with less severe fatigue, and the combination of severe fatigue and pain seems to have a larger impact on daily functioning than pain alone.[132] The included patients had fatigue levels comparable to patients with EDS (mean 37.0 vs 41.7). However, the proportion of the current HSD patients above the threshold of being severely fatigued (≥ 35 points) was lower than in patients with hEDS (61% vs 84%), suggesting an area where patients with HSD may differ from patients with hEDS.[132] Whether the level of fatigue is clinically relevant depends on an overall assessment that, besides looking at the threshold in CIS, should also include a clinical interview with the patient.[133]

Pain and fatigue seem to contribute to the disease burden in this patient group, further supported by the low health status scores (EQ-5D-5L) reported here compared with asymptomatic populations.[134] Although the observed TSK-11 scores were lower than previously reported scores in people with chronic pain,[135] half of the patients scored higher than the cut-point indicating high fear of movement.[136] Interestingly, this is more common than in patients with recurrent anterior shoulder dislocations, which may indicate that fear of movement is a substantial problem for some of the patients with HSD and shoulder complaints.

The finding that patients with mechanical shoulder symptoms were younger than those without corresponds well with the fact that the prevalence of GJH in both sexes decreases with age.[14, 137] Their different medical profiles in those with and without mechanical symptoms (e.g., regarding previous shoulder dislocations and feeling shoulder is loose) correspond well with shoulder dislocations being more prevalent in young individuals, which may compromise the glenoid labrum thereby decreasing passive structural joint stability.[51 52-54] This may result in repeated episodes of joint sprains, recurrent and subsequently chronic instability, and microtrauma, which may explain the longer symptom duration and higher healthcare utilisation in this subgroup.[138-140]

None of the selected objective characteristics could predict the presence of mechanical shoulder symptoms, which could suggest that other variables not included in this PhD thesis may be important. Factors that may contribute to experiencing mechanical shoulder symptoms are poor activity and function of the scapular and rotator cuff muscles, which have the potential to affect scapulohumeral coordination and lead to altered movement patterns due to the inherent soft tissue laxity.[47 46] These factors would require objective measurements of muscle activity, muscle recruitment, scapulohumeral coordination, or humeral translation to understand the underlying mechanisms further.

Effectiveness of progressive high load strength training

Paper IV

HEAVY led to greater improvements in self-reported shoulder function than LIGHT at 16-week follow-up. 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" (GPE). No serious adverse events were reported, but more patients undergoing HEAVY experienced transient muscle soreness and headaches.

Although the rationale for using HEAVY was to pose active joint stability to compensate for the lack of passive stability in hypermobile shoulders (Paper II), the mechanisms behind the effect of HEAVY seem to be complex and include psychosocial aspects and contextual effects.[141 142] The current non-significant findings regarding the

between-group difference in muscle strength in favour of HEAVY (scaption 10.4%, external rotation 12%) and positive clinical shoulder tests (an indirect measure of muscle-tendon stiffness) may partly explain the benefits of HEAVY on self-reported shoulder function and decreased physical symptoms. Other mechanisms that may have contributed to the benefits of HEAVY are the benefits of graded exercise to restore the ability of daily activities. This could potentially result 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 (e.g., significant changes were reported for the WOSI emotions subdomain).[97, 143]

No serious adverse events were reported in the RCT. Patients in both exercise groups experienced minor adverse events, but HEAVY led to more transient muscle soreness and headaches, known as acceptable adverse events in exercise-based interventions.[144] From a physiological perspective, muscle soreness can be seen as an important response to high load strength training that should not be a barrier to successful treatment outcome.[145]

Methodological considerations

Paper I-IV

Eligibility criteria

The diagnosis of HSD is ultimately clinical and requires no imaging or laboratory tests for confirmation. [30] Regional and national variations in the inclusion criteria in research studies and diagnostic criteria in clinical settings may be observed. Limitations of the eligibility criteria used are that this PhD thesis covers only one part of the patient group diagnosed with HSD, those with actual/historical GJH and shoulder complaints, and not those fulfilling two of the other four sub-classifications of HSD (Peripheral-HSD and Local-HSD). As described, the reason was to include a homogeneous group of patients with inherent/congenital GJH and not patients with only acquired local shoulder hypermobility.

As described, patients with hEDS were expected to have a formal medical diagnosis prior to participation in the studies, besides fulfilling the criteria for GJH and musculoskeletal manifestations. However, it turned out that none of the included patients had a diagnosis of hEDS. Therefore, the recruited population does not include hEDS. Although some similarity with HSD is found for patients with hEDS and other instability conditions, clear conclusions on these conditions must be drawn based on thorough investigations performed on these respective populations. When interpreting and generalising the current findings to other contexts, these caveats should be considered.

A combination of the Beighton score and 5PQ was initially used in this thesis to classify patients with GJH before making a formal diagnosis of HSD if significant joint hypermobility and musculoskeletal symptoms were present (and connective tissue diseases except hEDS were absent). The validity of using the Beighton score as a screening tool can be discussed; using an arbitrary cut-off of at least four for GJH has low sensitivity, high specificity, and a 60% false-positive rate.[11] The diagnostic validity improves by using age- and sex-specific cut-off scores as utilised in this thesis. Further, the 5PQ with a cut-point of at least two has been shown to correctly identify 84% of all cases with symptomatic GJH and healthy controls.[93] No specific shoulder hypermobility tests were included as part of the eligibility criteria because it was anticipated that many patients with shoulder complaints at inclusion would present with movement restrictions in their affected shoulder induced by their pain or symptoms. Therefore, using a shoulder specific test as an eligibility criterion would result in exclusion based on false criteria. Overall, the diagnostic accuracy for HSD is debatable, which may have impacted the current case definition.

Primary outcome

The WOSI questionnaire was used as the primary outcome of the RCT study (Paper IV), being the only shoulder related questionnaire covering instability symptoms translated to Danish. The WOSI questionnaire was designed for self-assessment of shoulder function in patients with symptomatic shoulder instability, defined as "*the loss of shoulder comfort and function due to undesirable translation of the humeral head on the glenoid*."[97] As reported in Paper III, 67% of the 100 patients in the RCT (Paper IV) reported mechanical shoulder symptoms. Furthermore, 54 patients fulfilled the criteria for a clinical diagnosis of anterior shoulder instability, 78 patients for MDI, and 90 patients had at least one positive shoulder hypermobility test. Therefore, the questionnaire is considered relevant in patients with HSD and shoulder complaints. The WOSI is responsive and sensitive to change as well as being a valid questionnaire, with a high test-retest reliability, justifying its use as the primary outcome.[99, 127]

Self-reported mechanical symptoms

The definition used to establish the presence of self-reported mechanical shoulder symptoms has not been validated, which is important for future clinical and research use. However, the rationale for including self-reported mechanical symptoms as a supplemental characteristic is that there is a difference between being clinically diagnosed with shoulder instability and having the experience of mechanical symptoms. For the knee, it has been reported that there is no clear association between being identified with a clinical knee diagnosis and the subjective experience of mechanical symptoms;[100, 101] half of the patients with subjective mechanical symptoms did not have a meniscal lesion, which researchers previously thought was the case. This might indicate that sometimes subjective symptoms cannot be identified in clinical

diagnoses and potentially be overlooked. In line with this knowledge on the knee, it was anticipated that this lack of an association also applied to a clinical shoulder diagnosis of shoulder instability such as MDI or anterior instability and the subjective experience of mechanical shoulder symptoms.

Interventions

The two interventions in the RCT are of varying complexity in terms of training and delivery. One of the major differences is the number of supervised sessions between groups: patients in HEAVY could get up to 32 supervised sessions, while patients in LIGHT consulted a physiotherapist up to three times during the intervention. Because HEAVY is a new exercise approach, it was deemed important to provide intensive supervision to manage potential adverse events and adequate load progression. This was less important in LIGHT, where exercises were performed without getting fatigued and with low loads. Although a recent systematic review has shown that supervised exercise and unsupervised exercise are equally effective in patients with shoulder complaints,[146] the difference in delivery in the current RCT-study and the associated difference in contextual effects and attention bias could potentially explain the between-group differences (Paper IV). Presumably, the patients in LIGHT would be expected to have a greater effect than self-training or no training because they received three individual supervised sessions. Furthermore, HEAVY includes full range, high load, open kinetic chain exercises, while LIGHT includes primarily static, neutral or mid-range, low load, closed kinetic chain exercises. Therefore, the exercise programmes compare different concepts rather than just one element related to the amount of loading, making it difficult to conclude that the observed benefits in HEAVY compared with LIGHT are due to the high load component alone.

The exercise interventions in this PhD thesis focus primarily on a single joint, although patient education about the HSD condition and load management in daily activities was also included. The reason for this approach was because the included patients primarily had shoulder complaints and due to pragmatic and practical reasons for conducting a large-scale RCT in primary care, where the interventions must be readily applicable to the daily work of the physiotherapists, e.g., the intervention should typically last for maximally 30 minutes per session. However, considering that patients with HSD/hEDS commonly have complaints in several joints as well as suffering from comorbidities related to joint hypermobility and psychological distress,[30, 37] it is recommended to use 'whole body' management (rather than individual joints or body areas) in addition to focusing on self-management approaches for long-term conditions.[57, 147] As such, it is important to consider these caveats of using a single joint exercise programme such as the HEAVY programme when implementing the programme to patients in clinical practice.

Besides patient education and intensive supervision to manage potential symptom flares, the RCT did not employ manual therapy or other physiotherapy modalities to gain short-term relief (e.g., headaches) that could have increased exercise adherence or allowed larger increases in load.[148, 149] However, the current findings can neither recommend nor discourage the use of additional physiotherapy modalities as an adjunct to the HEAVY programme.

The long-term follow-up at 12 months is part of the RCT (Paper II), and it is highly relevant to see if these findings confirm the findings at 16 weeks. Furthermore, it was not within the scope of this study to evaluate the cost-effectiveness of the interventions. Still, it may be conducted later using the Danish national registries to further inform the clinical decision-making in treating patients with HSD and shoulder complaints.

Short-term clinically relevant improvements

Paper II, IV

The minimal important change has previously been defined as 10.4%[98] and 14%[121], corresponding to 218.4 and 294 points on the WOSI total score, respectively. In the absence of a patient-derived minimal important difference (MID), the MID was a priori defined as between-group differences of at least 12% (252 points). The mean between-group difference postintervention (8.3%, 174.5 points) was statistically significant but below the MID, while the per-protocol analysis reached the MID (11.9%). These findings are in line with between-group differences in WOSI (11.1% at 12 weeks) in a study on MDI that favoured a progressive shoulder strengthening exercise programme with regard to load and range of motion compared with strengthening mainly in 0 degrees of elevation.[64] When interpreting the results, it is important to consider that the available MID thresholds are based on within-group changes and that the MID should be applied to changes in the number of individual patients and not only group changes.[150, 151] A post hoc analysis supported that a larger proportion of patients in HEAVY (ITT 68%, per protocol 85%) than in LIGHT (ITT 54%, per protocol 55%) reached improvements above 12% in the WOSI total score. Overall, the clinical relevance of the between-group difference remains partly unclear.[152] However, these findings add to the debate regarding the relevance of prescribing additional doses of shoulder strengthening as a treatment for shoulder conditions, indicating that progressive high load strength training is relevant for the current patient group with HSD and shoulder complaints.[153-155]

Limitations and strengths

Paper I

Due to the inherent design of a feasibility study, methodological limitations such as lack of a control group and inability to ensure blinding of patients and investigators,

limited conclusions could be drawn on the treatment effectiveness. The observed improvements in secondary outcomes could be due to regression to the mean. The strengths of the feasibility study were the standardised, predefined, transparent, and precisely described research progression and evaluation criteria that informed the design of the RCT study.

Paper III

The limitations of this study were attributed to the descriptive design: no conclusions could be drawn about the cause-relationship of the findings, and the included clinical characteristics were only a sample of the many clinical characteristics that potentially can predict the presence of mechanical shoulder symptoms. Furthermore, mechanical shoulder symptoms were self-reported without a subsequent objective comparison (e.g., assessment of positional/non-positional and voluntary/involuntary instability)[48] or imaging verification of potential structural defects.

The strengths were that data was collected by blinded assessors not otherwise involved scientifically in the study. The primary analyses were predefined and published before conducting the analyses (Appendix 1) and supplied with exploratory analyses when relevant. The reporting follows STROBE guidelines for cross-sectional studies.

Paper II, IV

This trial had limitations. The LIGHT programme was developed as an active comparator to mimic the average exercise-based standard treatment offered across physiotherapy clinics in Danish primary care. Since there is a large variation in treatments among clinicians, the patients could potentially have been offered a better or worse treatment than they would have received typically. However, LIGHT is considered a better approach than wait-and-see or no treatment for this patient group.[84, 155] Although patients and treating physiotherapists were not blinded, both interventions were presented as having the potential to be effective.

This trial had many notable strengths. The pragmatic approach of this study using broad eligibility criteria, a consecutive sampling strategy, usual care as the comparator, and patients recruited from primary care improve the generalisability. The pre-registration at ClinicalTrials.gov and publication of the a priori study protocol (Paper II), statistical analysis plan (Appendix II), blinded interpretation of the findings (Appendix III), and thoroughly described exercise protocols based on established frameworks greatly improve the overall quality of the current study and the potential for implementation.

Key points

- **WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?**

Patients with HSD are at great risk of experiencing persistent shoulder complaints such as chronic pain and mechanical shoulder symptoms, but evidence for effective treatment is sparse.

- **WHAT DOES THIS PHD THESIS ADD?**

A progressive high load shoulder strengthening exercise programme is feasible and tolerable as a structured treatment for patients with HSD.

Patients with HSD from primary care included in a multi-centre RCT had substantial impairments related to shoulder pain, function, fatigue, fear of movement, and quality of life. Two-thirds of the patients reported mechanical shoulder symptoms. These patients were younger and more severely impaired than those without mechanical shoulder symptoms.

Sixteen weeks of supervised progressive high load shoulder strength training was statistically superior to 16 weeks of less supervised and less progressive low load exercises (usual care) on self-reported shoulder function and shoulder-related quality of life. However, the clinical relevance of the between-group differences remains unclear, and the secondary supportive outcomes were generally inconclusive with wide confidence intervals.

- **HOW MIGHT THIS IMPACT CLINICAL PRACTICE AND FUTURE DEVELOPMENTS OF EFFECTIVE CARE?**

The findings highlight the importance of addressing mechanical shoulder symptoms during assessment and treatment to understand the patients' impairments fully.

Progressive high load strength training may potentially be effective as treatment in patients with HSD and shoulder complaints to reduce symptoms and improve shoulder function in the short term. Clinicians should pay attention to and help alleviate the minor transient symptoms following the treatment. However, further research using robust methods should investigate the clinical relevance of the current between-group differences, explore the underlying mechanisms supporting any potential benefits, and confirm the findings in long-term follow-ups.

Conclusions

This PhD thesis investigated patients with HSD and persistent shoulder complaints and the effectiveness of supervised progressive high load strength training as treatment. All progression criteria for a future RCT were met using a feasibility study, except the recruitment rate that was optimised before finalising the protocol and conducting the RCT with the inclusion of 100 patients from primary care.

The included patients presented at baseline with substantial shoulder-related impairments, and two-thirds of patients with self-reported mechanical shoulder symptoms were more severely affected. These findings provide the initial data to support addressing mechanical symptoms in the shoulder during treatment to fully cover and understand the patients' impairments.

The conducted RCT demonstrated the effectiveness of the high load strengthening programme in improving shoulder symptoms and function at the primary endpoint 16-week postintervention. However, the secondary supportive outcomes were inconclusive making it challenging to explain the potential underlying mechanisms supporting any potential benefits. Further, more studies using transparent, detailed, and high-quality methods to confirm the clinical relevance and the long-term effects are needed before full implementation of the results is justified.

Overall, supervised progressive, high load strength training may be used as a safe treatment in patients with HSD and shoulder complaints in a primary care setting to reduce symptoms. It may also improve shoulder function in the short term, as it was statistically superior to less supervised and low load strengthening exercise. This is important because a high load training protocol may potentially improve future clinical practice and treatment of the critical and severe condition of HSD.

Perspectives and clinical implications

Patients with shoulder problems are commonly referred to primary and secondary care due to severe and persistent functional impairments affecting their daily activities and health-related quality of life. Clinicians who examine patients with shoulder complaints should start the examination with tests and questions to rule out or rule in the presence of joint hypermobility (e.g., GJH) to capture those patients fulfilling the criteria for HSD (or hEDS). Secondly, it is suggested that patients with HSD and shoulder complaints should be interviewed about any mechanical shoulder symptoms, in addition to pain, general discomfort, and fatigue. Besides considering symptom duration (the current median symptom duration being 39 months) and age, questions related to the feeling of the shoulder being loose and previous episodes of shoulder dislocations are suggested to be included in the history taking. Further, when assessing symptom severity, pain assessments should be accompanied by questions specifically focusing on discomfort due to other symptoms since no other included self-reported or objective characteristics in Paper III showed an association with experiencing mechanical shoulder symptoms.

The HEAVY programme was used by physiotherapists from primary care who were allowed to modify the programme to fit the individual patient. The HEAVY programme is specifically developed for this PhD thesis, and the findings are based on group results. Individual patients may need modifications such as a more extended familiarisation period, longer recovery between sessions (e.g., exercise twice instead of three times a week), intervention periods longer than 16 weeks, additional or alternative exercises, less or more supervision, or supplementary manual treatment for short-term pain relief. This PhD thesis does not provide firm concluding data about the above alterations in the training programme. However, with each patient, it is the responsibility of the individual care provider to consider these aspects of delivering the progressive high load strength training programme as presented here.

Future studies should investigate the role of other relevant characteristics (e.g., muscle activity, joint translation) in patients with and without self-reported mechanical symptoms and use objective measures of mechanical shoulder symptoms to distinguish between these subgroups. Furthermore, the use of progressive high load strength training should be investigated in patients with hEDS using a feasibility design (since none of the included patients in this PhD thesis had a formal diagnosis of hEDS) to evaluate if they can tolerate supervised progressive high load strength training, before conducting an RCT on treatment effectiveness. Implementing progressive high load strength training should also be investigated in sports athletes, e.g., swimmers with HSD and shoulder complaints, who generally have an existing high load component from their sports-specific practice and competition.

The wide CIs in the RCT (Paper IV) may indicate that the sample size was too small, which is why the conclusions from the data need to be replicated with larger sample size and a long-term follow-up, as well as investigating the applicability of these findings in different international/cultural settings. It will be relevant to investigate progressive high load strength training as part of a 'whole body' management. More knowledge about phenotypes and mechanisms behind high load strength training in this patient group is needed.

Lastly, this PhD thesis questions current international guidelines that recommend low load exercises. This PhD thesis suggests that supervised progressive high load strength training is a viable alternative as part of the clinical repertoire in improving shoulder pain, function, and quality of life in the short term when promoting individually tailored exercises and load in patients with HSD and persistent shoulder complaints. If the results in the present study are confirmed or supported in future trials, current international guidelines need to be updated accordingly.

List of figures and tables

Figures

Tables

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Consent for publication

Written consent for the publication of images was obtained.

Availability of data and material

The datasets generated and analysed during this PhD thesis are available from the author on reasonable request.

Competing interests

STS reports personal fees from the Journal of Orthopaedic & Sports Physical Therapy, grants from The Lundbeck Foundation, private fees from Munksgaard, outside the submitted work, and being co-founder of GLA:D. GLA:D is a non-profit initiative hosted at the University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice. JS reports grants from AstraZeneca outside the submitted work. BL, KS, EB, UF, and BJK have nothing to disclose.

Appendices