LOW-INTENSITY, HIGH-FREQUENCY HOME-BASED STRETCHING FOR FIBROMYALGIA

FROM MECHANISTIC RATIONALE TO FEASIBILITY AND CLINICAL EVALUATION OF EFFECTS

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CV

Morten Pallisgaard Støve works as an Associate Lecturer at the Department of Physiotherapy at University College of Northern Denmark (UCN) and was enrolled as a PhD student in September 2022 at the Center for General Practice at Aalborg University. His academic training includes a BA in Physiotherapy (2007) and an MSc in Clinical Science and Technology (2016), which provide the foundation for his work in rehabilitation science. His doctoral research investigates stretching-based interventions in fibromyalgia, examining clinical outcomes, particularly quality of life, alongside changes in pain sensitivity. By integrating mechanistic approaches to pain processing with applied clinical research, he aims to develop and evaluate a home-based, scalable rehabilitation programme that is feasible to deliver within routine care.

English Summary

Fibromyalgia (FM) is a nociplastic pain condition associated with widespread pain and substantial multisymptom burden. Because no curative treatment exists, clinical management relies on multimodal strategies combining education, psychological interventions, and physical exercise. Yet many individuals experience exercise intolerance and difficulty sustaining long-term adherence, underscoring the need for feasible and tolerable low-burden exercise modalities. Stretching may represent a low-impact option and has been proposed to influence pain sensitivity via central pain modulation; however, at the outset of this PhD, the evidence for stretching in FM was fragmented and methodologically heterogeneous, limiting conclusions regarding optimal prescription parameters, stretching approaches, delivery formats, and clinical benefit.

The overall aim of this thesis was to develop and clinically evaluate a mechanistically grounded, low-intensity, high-frequency home-based stretching intervention for FM that is feasible and acceptable, and to determine whether it can improve FM-relevant outcomes compared with usual care. To achieve this, Studies I–V formed a staged programme progressing from mechanistic work in healthy adults to feasibility testing and clinical evaluation in FM, with each study informing the subsequent stage of intervention development and evaluation. Mechanistic studies examined whether repeated stretching is accompanied by time-dependent adaptations in pain sensitivity and whether acute stretch-induced hypoalgesia depends on stretching intensity. A systematic review synthesised the current evidence on stretching in FM, assessing clinical efficacy and key methodological limitations relevant for clinical translation. A feasibility study evaluated the acceptability and delivery features of the home-based protocol, relevant to participant experience and engagement, and informed refinements to intervention materials and procedures before clinical evaluation. mHealth tools were used across relevant studies to support standardised delivery through video instruction, prospective session logging, and participant-investigator communication.

Regular stretching was associated with reductions in regional and widespread pain sensitivity in healthy adults, with effects maintained following a cessation period, supporting the mechanistic plausibility of repeated stretching as a pain-modulatory stimulus. This is consistent with existing evidence suggesting that repeated stretching can reduce pain sensitivity.

Across the tested intensity range, increasing stretching intensity towards pain onset did not elicit greater acute hypoalgesia than an intensity defined by a clear stretch sensation, supporting a non-painful intensity target for clinical translation in FM, where exercise tolerability and symptom response are central. The evidence synthesis indicated that stretching trials in FM generally favoured improvement but were supported by very low-certainty evidence and substantial methodological heterogeneity, reinforcing the need for a clearly specified protocol. The home-based low-intensity, high-frequency protocol was feasible and acceptable in FM, and the feasibility findings informed refinements to intervention materials and study procedures before clinical evaluation. Within the trial timeframe, the clinical evaluation indicated that the home-based stretching protocol was associated with improvements in FM-relevant symptom impact and related patient-reported outcomes compared with usual care.

In conclusion, this thesis establishes a mechanistically informed, standardised home-based stretching protocol for FM, with evidence of short-term clinical improvement compared with usual care. Although conclusions about longer-term benefit are limited by the open-label context and the lack of extended between-group follow-up, the findings warrant confirmatory evaluation of the durability of the effects and pragmatic implementation strategies in broader FM populations.

Resume in Danish

Fibromyalgi (FM) er en nociplastisk smertetilstand, som er forbundet med generaliserede smerter og en betydelig samlet symptombyrde. Da der ikke findes en kurativ behandling, baseres behandlingen på multimodale strategier. Disse omfatter bl.a. patientuddannelse, psykologiske interventioner og fysisk træning. Mange patienter oplever imidlertid træningsintolerance og har vanskeligt ved at fastholde træning over tid. Det understreger behovet for at udvikle nye, overkommelige træningstilbud. Udspænding kan være en skånsom træningsform, og den nuværende evidens peger på, at udspænding kan påvirke smertesensitiviteten gennem central smertemodulation. Ved opstarten af denne ph.d.-afhandling var evidensen for udspænding ved FM imidlertid fragmenteret og metodologisk heterogen. Der var derfor et begrænset grundlag for at drage sikre konklusioner om optimal dosering, udspændingsmetode og potentiel klinisk effekt.

Formålet med denne ph.d.-afhandling var at udvikle og klinisk evaluere en lav-intensiv, hjemmebaseret udspændingsintervention til personer med FM. Desuden blev det undersøgt, om interventionen kan forbedre FM-relevante outcomes i forhold til vanlig behandling. Ph.d.-afhandlingen var opbygget i successive faser, så hvert studie byggede videre på det foregående. Studie I–V omfattede således først mekanistiske studier i raske populationer og derefter feasibility-afprøvning samt klinisk evaluering hos patienter med FM. De mekanistiske studier undersøgte, om regelmæssig udspænding medfører vedvarende ændringer i smertesensitiviteten, og om akut udspændingsinduceret hypoalgesi afhænger af udspændingsintensiteten. Herefter blev et systematisk review gennemført for at sammenfatte evidensen fra randomiserede kontrollerede studier. Reviewet vurderede både den kliniske effekt af udspænding ved FM og de metodologiske begrænsninger, der har betydning for den kliniske anvendelse. Dernæst blev der gennemført et feasibility-studie, som vurderede, om en hjemmebaseret udspændingsprotokol var gennemførlig og acceptabel, samt hvilke forhold der havde betydning for patienternes oplevelse og accept af interventionen. På baggrund af resultaterne blev interventionen, informationsmaterialet og studieprocedurerne justeret. Herefter blev der gennemført en endelig klinisk evaluering, hvor interventionens effekt blev undersøgt. I flere af studierne

blev en sundhedsapp brugt til standardiseret levering via videoinstruktion, træningsregistrering og kommunikation mellem deltager og forsker.

Resultaterne viste, at regelmæssig udspænding var associeret med reduceret regional og generel smertesensitivitet hos raske voksne, og at effekterne blev fastholdt efter en periode uden udstrækning. Dette understøtter den eksisterende evidens for, at gentagen udspænding kan reducere smertesensitiviteten. Der sås ikke større akut hypoalgetisk effekt ved udspænding til fornemmelsen af smerte end ved udspænding til fornemmelsen af stræk. Det underbygger anvendelsen af et ikke-smertefuldt intensitetsmål i FM, hvor det er afgørende, at interventionen kan tolereres. Det systematiske review viste overordnet en tendens til forbedring ved udspænding hos personer med FM. Evidensen var dog præget af meget lav sikkerhed og betydelig metodologisk heterogenitet, hvilket understreger behovet for en klart specificeret udspændingsprotokol. Den hjemmebaserede lav-intensive udspændingsprotokol var gennemførlig og acceptabel hos personer med FM. Feasibility-resultaterne blev brugt til at justere interventionen, informationsmaterialet og studieprocedurerne før den kliniske evaluering. Sammenlignet med vanlig behandling var lav-intensiv udspænding associeret med forbedringer i FM-relevante patientrapporterede outcomes, inden for forsøgsperioden.

Samlet set præsenterer denne afhandling en mekanistisk informeret standardiseret hjemmebaseret udspændingsprotokol til personer med FM. Afhandlingen bidrager desuden med evidens for en signifikant klinisk forbedring sammenlignet med vanlig behandling. Fortolkningen af længerevarende effekter begrænses af dog af det åbne design og den manglende opfølgning. Derfor er der behov for yderligere forskning i effekternes varighed samt pragmatiske implementeringsstrategier i bredere FM-populationer.

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Most importantly, I would like to thank all participants, both the individuals living with fibromyalgia and the healthy volunteers, who contributed their time, effort, and trust. Their willingness to participate made this research possible. I also acknowledge the value of the patient and public involvement during the project's development, which helped sharpen priorities and the ethical framing of the trial.

I would also like to thank my co-authors for their contributions across the work underpinning this thesis. In particular, I am grateful to Anne Mette Lücke Dissing, Louise Landbo Larsen, Line Ørum Hansen, and Kristian Kloppenborg Elmbæk.

Finally, to my wonderful wife and our two daughters. When I began the PhD, I promised myself that it would not be at the expense of time spent with you. I therefore hope that I have managed to remain present, engaged, and no more irritating than usual.

List of papers

This PhD thesis is based on the following five articles, which are hereafter referred to by their Roman numerals in the text.

Study I

Støve, M.P., Thomsen, J.L., Magnusson, S.P. et al. The effect of six-week regular stretching exercises on regional and distant pain sensitivity: an experimental longitudinal study on healthy adults. BMC Sports Sci Med Rehabil 16, 202 (2024). https://doi.org/10.1186/s13102-024-00995-2 (Appendix A)

Study II

Støve, M.P., Dissing, A.M.L., Thomsen, J.L. et al. The effectiveness of stretching exercises in patients with fibromyalgia: A systematic review. Clin Rheumatol 43, 3039–3053 (2024). https://doi.org/10.1007/s10067-024-07066-4 (Appendix B)

Study III

Støve, M. P., Hansen, L. Ø., Elmbæk, K. K., Magnusson, S. P., Thomsen, J. L., & Riis, A. (2025). The effect of stretching intensity on pain sensitivity: A randomized crossover study on healthy adults. European Journal of Pain, 29, e4750. https://doi.org/10.1002/ejp.4750 (Appendix C)

Study IV

Støve, M.P., Larsen, L.L., Magnusson, S.P. et al. Exploring the feasibility, acceptability and preliminary efficacy of a Home-Based stretching program for adults with fibromyalgia: a prospective Pre-Post feasibility study. Rheumatol Int 45, 191 (2025). https://doi.org/10.1007/s00296-025-05921-4 (Appendix D)

Study V

Støve, M. P., Magnusson, S. P., Thomsen, J. L., & Riis, A. Efficacy of a novel home-based stretching program on fibromyalgia symptoms: a randomised controlled trial. In review. (Appendix E)

Related publications

Additional contributions related to this PhD thesis by the author are listed below.

Støve, M.P., Dissing, A.M.L., Thomsen, J.L. et al. A rebuttal to "The ineffectiveness of stretching exercises in patients with fibromyalgia: A systematic review discussion" — comments on "The effectiveness of stretching exercises in patients with fibromyalgia". Clin Rheumatol 44, 529–530 (2025). https://doi.org/10.1007/s10067-024-07223-9 (Appendix F)

Støve, M. P., Hansen, L. Ø., Elmbæk, K. K., Magnusson, S. P., Thomsen, J. L., & Riis, A. (2025). Authors' reply to the comment by Zhu et al. European Journal of Pain, 29, e4770. https://doi.org/10.1002/ejp.4770 (Appendix G)

Støve, M.P., Magnusson, S.P., Thomsen, J.L. et al. Efficacy of a home-based stretching programme on fibromyalgia symptoms: study protocol for a randomised controlled trial. Trials 26, 74 (2025). https://doi.org/10.1186/s13063-025-08776-z (Appendix H)

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Chapter 1. Background

Fibromyalgia

Fibromyalgia (FM) is a complex pain syndrome, characterised by chronic widespread pain and generalised hyperalgesia [1,2]. Although the concept of FM dates back to the 19th century, the American College of Rheumatology (ACR) first proposed formal diagnostic criteria in 1990 [3]. Over time, these criteria have been revised, with the most recent iteration published in 2016 [4]. Despite these refinements, aspects of FM, particularly its pathophysiology and diagnostic boundaries, remain debated [3]. Accurately diagnosing FM can be challenging, as there are no radiological, biochemical or histological tests to assist clinicians [1]. Although FM has historically been described as a diagnosis of exclusion, contemporary criteria emphasise a symptom-based clinical diagnosis while still requiring careful assessment for competing diagnoses [4,5].

According to the 2016 ACR criteria, a diagnosis of FM requires the following. Symptom burden must meet specified Widespread Pain Index (WPI) and Symptom Severity Scale (SSS) thresholds, defined as either WPI $\geq$ 7 with SSS $\geq$ 5, or WPI 4–6 with SSS $\geq$ 9 [4]. Generalised pain must be present in at least four of five body regions, excluding jaw, chest, and abdominal pain from this definition [4]. Symptoms must have been generally present for at least three months, and the diagnosis may be made irrespective of other coexisting conditions, as FM does not exclude other clinically important illnesses [4].

Prevalence estimates for FM vary substantially depending on the specific diagnostic criteria used, with reports ranging from approximately 2% to 8% of the general population [4]. It is estimated that FM affects up to one in 20 patients in primary care [6]. But increased awareness of FM may contribute to higher rates of diagnosis and healthcare utilisation [7]. FM has a female predominance [4], and the major view has been that most FM diagnoses occur in women [8]. Recent epidemiological data using the 2016 criteria indicate that females are approximately twice as likely as males to be diagnosed with FM [9], suggesting that the degree of sex difference may be smaller than previously assumed. Nonetheless, FM is still considered the leading cause of generalised musculoskeletal pain in women [9].

Pain is the defining feature of FM [10]. Beyond pain, other significant symptoms of FM are fatigue, sleep disturbance, cognitive symptoms, and

psychological symptoms, contributing to reduced daily functioning and quality of life [11]. FM is also associated with poor quality of life, increased prevalence of diabetes, poor self-rated health, increased illness worry and extensive utilisation of medical services [12–14]. Symptom severity can fluctuate substantially over time and may vary with contextual factors, such as activity levels, contributing to variability in disease burden [15,16].

People with FM commonly exhibit intolerance to physical activity [10]. Consequently, they are more likely to engage in sedentary behaviours, which have been linked to an increased incidence of secondary health problems, including cardiovascular and metabolic disorders [17,18].

FM is a debilitating disorder associated with increased risk of depression, suicidal behaviour, and chronic disability [19]. The societal consequences of FM are substantial, with high levels of absenteeism and unemployment. In Denmark, only one in five patients is still part of the workforce ten years after symptom onset [20,21]. This considerable individual and societal impact must be viewed in the context of the complex pathophysiology and pronounced clinical heterogeneity of FM, which are considered in the following sections

Pathophysiology and Clinical Heterogeneity

FM is currently classified as a nociplastic pain condition [22]. The International Association for the Study of Pain (IASP) defined nociplastic pain as *"pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somato-sensory system causing the pain." [23].* The aetiology of FM remains unknown, but its pathophysiology is considered complex, as multiple interacting mechanisms are proposed to shape its clinical presentation and pathophysiology [11,24]. Evidence suggests that numerous modulating factors influence the clinical expression, including peripheral immune mechanisms, changes in the autonomic nervous system, neuroinflammation, central sensitisation, and changes in the gut microbiome. In addition, contextual psychosocial factors and lived experiences are also known to modulate the clinical representation of FM [22,25,26]. Consequently, FM is a condition characterised by significant inter-individual symptom variability [27].

Despite the complexities in its pathophysiology, central sensitisation is still considered the main driver of FM [1,28]. The exact mechanisms underlying nociplastic pain remain unclear. Nevertheless, nociplastic pain is commonly attributed to altered central processing and dysregulated modulation of nociceptive signalling [2,29]. In FM, evidence suggests reduced endogenous inhibitory control, consistent with impaired descending pain inhibition and greater pain sensitisation [30–32].

Descending pain modulation regulates nociceptive processing through both inhibitory and facilitatory influences originating from different cortical and brainstem regions [33,34]. Descending pain modulation is mediated by neural circuits spanning cortical, subcortical, and brainstem regions, including the prefrontal cortex (PFC), anterior cingulate cortex (ACC), periaqueductal grey (PAG), and rostral ventromedial medulla (RVM) [34]. Via endogenous neurotransmitters such as serotonin, noradrenaline, dopamine, and opioids, these pathways modulate nociceptive input at the dorsal horn by suppressing or facilitating pain signalling [35]. Descending pain modulation exerts both inhibitory and facilitatory influences on nociceptive input, and evidence suggests that this balance may shift towards facilitation in FM, reflecting reduced inhibitory control that may contribute to the persistence of pain [30,32]

Although FM is primarily characterised by altered central pain processing, evidence also points to autonomic dysregulation that may be associated with pain severity and symptom burden in FM [36,37]. In FM, hypothalamic-pituitary-adrenal axis dysfunction is frequent, indicating an imbalance in the body's stress response system, which is often related to chronic stress [11,38,39]. This dysfunction, characterised by abnormal cortisol levels and stress reactions, is linked to impaired stress responses and altered pain regulation [32,40]. Likewise, studies have demonstrated a relationship between pain intensity and sympathetic overactivity [37] indicating that lower parasympathetic activity is associated with higher pain intensity [41]. In addition, studies have shown that symptoms such as insomnia and non-restorative sleep may also be directly related to sympathetic hyperactivity in FM [42].

In addition, several lines of evidence also show that factors like the immune system, neuroinflammation, genetic aspects, as well as psychosocial and endocrine factors, may all modulate the clinical representation of FM [1,11].

Taken together, this highlights the multidimensional and heterogeneous nature of the symptom burden in FM. This presents a significant barrier to effective treatment, suggesting that one-size-fits-all approaches are unlikely to be successful.

Implications for FM Treatment

For FM, no curative treatment is available [1,11,43]. Current management, therefore, focuses on symptom reduction and improving function and quality of life [5,44].

The heterogeneity of FM complicates management because symptom profiles and treatment responses vary substantially between individuals [11]. Pharmacological approaches are frequently employed in the management of FM [45]. However, previous research has established that pharmacological treatment alone is often insufficient to achieve meaningful symptom improvement [1,11]. An overview of Cochrane reviews concluded that evidence for many medications in FM is limited, with only duloxetine, milnacipran, and pregabalin showing substantial short-term pain relief in 1-10 adults with moderate to severe pain [46].

More recently, low-dose naltrexone and cannabinoids have been proposed as potential options, due to their potential to function as a neuroinflammatory modulator and their suggested pain-relieving effects [22,45]. However, there is a lack of evidence for their analgesic efficacy in FM [47–49]. Overall, pharmacological treatments provide, on average, small-to-modest effects on FM symptoms [1,11,22,39,44].

Although efficacy is limited, pharmacological therapy remains a recommended component of multimodal FM management [2,22,50]. Guidelines consistently emphasise non-pharmacological approaches such as physical exercise, patient education, and cognitive behavioural therapy as the first-line approach, complemented by pharmacological options where appropriate [51–56] Nevertheless, evidence suggests that non-pharmacological treatments are underutilised in routine care, and that most patients with FM are managed with pharmacological measures alone [57].

This gap between guideline recommendations and routine practice underscores the need for non-pharmacological strategies that can be integrated into routine care, as well as exercise interventions that individuals with FM can tolerate and sustain.

Exercise Modalities for FM, Mechanisms, and Challenges

The following section summarises the existing body of evidence relevant to this topic at the onset of the present PhD study, drawing on contemporary references.

Current Evidence on Exercise-Based Interventions in FM

Patients with FM commonly report exercise intolerance and engage in lower levels of physical activity, which may contribute to physical deconditioning over time [10]. Although the causal role of deconditioning in FM remains uncertain, it is clinically relevant because reduced physical capacity can exacerbate functional limitations [58]. In FM, however, the rationale for exercise extends beyond conditioning to include symptom modulation and maintenance of everyday functioning.

Among non-pharmacological strategies for FM, structured exercise has received the most consistent empirical support [2,59]. Contemporary recommendations typically encompass aerobic (cardiorespiratory), resistance (muscle-strengthening), and flexibility-based modalities. Nevertheless, pooled effects are typically small to moderate, and interventions differ markedly in their design and delivery, limiting the ability to draw clear conclusions about optimal prescription parameters and clinical implementation [10].

Previous Cochrane reviews report small to moderate average effects of exercise therapies in FM [10,48]. Since these reviews, newer trials and contemporary syntheses have consistently reported more positive effects on key outcomes like pain and quality of life, supporting exercise as a core component of FM management [59,60]. Accordingly, current clinical guidelines strongly recommend individually graded aerobic and strengthening exercise for FM [2,51–54].

Mechanisms Underlying the Effects of Exercise in FM

Although aerobic and strengthening exercise can improve symptoms in FM, the mechanisms underlying these benefits remain incompletely understood [61]. Proposed explanations include pain-modulatory pathways (e.g., exercise-induced hypoalgesia (EIH) and altered central modulation) as well as broader effects on sleep and psychological factors such as self-efficacy [61]. Accordingly, this thesis focuses primarily on pain-modulatory mechanisms, while also considering autonomic regulation as a secondary mechanistic pathway.

With respect to autonomic regulation, exercise has been shown to influence the sympathetic nervous system by modulating the sympathovagal balance [62], which is mechanistically relevant given evidence of autonomic dysregulation in FM [38,39]. In healthy adults, exercise is typically associated with increased sympathetic and reduced parasympathetic activity, followed by post-exercise recovery. With training, vagal modulation may increase over time, leading to greater parasympathetic activity [54]. Regular exercise has been associated with improvements in autonomic regulation and sleep quality, although effects appear variable across conditions [62]. In addition, exercise may improve self-efficacy and mental health in clinical populations. However, the mechanisms are not well established and likely reflect multiple interacting factors [63]. However, emerging evidence suggests that exercise may modulate autonomic balance differently in chronic pain populations, which suggests limited generalisability from healthy adult responses [62]. Accordingly, exercise prescription in FM may require attention to dose and the mode of exercise rather than assuming responses observed in healthy adults [62].

Beyond the potential autonomic and psychological effects, exercise also appears to influence pain processing [64]. Exercise can reduce pain sensitivity through endogenous inhibitory mechanisms, although responses are variable and may be attenuated in chronic pain conditions [64,65]. However, exercise can also increase pain, suggesting that there may be a balance between endogenous inhibition and facilitation that determines whether exercise will promote analgesia or pain [65]. Several factors may affect this balance, including overall physical fitness, habitual activity

levels, and the presence of comorbid disorders or chronic pain syndromes, such as FM [65].

Although the evidence is not entirely consistent, current evidence suggests that the analgesic effects of exercise may exhibit an intensity-dependent dose-response relationship, with higher intensities generally associated with larger hypoalgesic effects [66–68]. This raises the question of how to prescribe exercise in FM to support analgesic responses without provoking symptom exacerbation.

In FM, endogenous pain modulation is often impaired, reflecting reduced efficiency of central inhibitory mechanisms [69], and this impairment has been linked to greater pain sensitisation [30]. This disrupted regulation may contribute to exercise intolerance in FM [28], where initiation of physical activity is frequently associated with intense symptom exacerbation [51]. Consequently, pain and fatigue often limit tolerance of exercise programmes and restrict sustained participation [28]. Against this background, adherence to exercise is often challenging, and many patients refrain from physical activity for fear of worsening symptoms [51]. Consequently, sustaining adherence to exercise remains a major challenge in FM management.

Barriers to Exercise Participation and Adherence in FM

Given that adherence is associated with a higher quality of life in FM [70], the success of exercise-based management depends not only on efficacy but also on the patient´s ability to sustain participation over time. However, adherence is more often constrained by symptom exacerbation and by practical barriers [70].

Patients with FM frequently report exercise intolerance, such that even modest physical activity can trigger disproportionate symptom exacerbation [28]. Exercise-induced symptom exacerbation, characterised by increased pain and fatigue after activity, is commonly reported following low- to moderate-intensity exercise [51,71]. Recurrent symptom flares following exercise may foster beliefs that exercise is harmful and promote avoidance behaviour [29], reducing habitual activity and potentially contributing to deconditioning and heightened sensitivity over time [72]. Collectively, these

observations suggest that moderate- or high-intensity exercise, often considered necessary to elicit meaningful benefits [68,73], may not be feasible for many individuals with FM.

In addition to barriers arising from fluctuating symptom severity and variability in functional capacity from day to day, structural constraints such as cost, travel, and time burden may also limit participation in exercise-based interventions [74,75]. Supervised programmes can also entail direct fees, travel-related expenses, and substantial time commitments, which may be prohibitive for individuals with limited financial resources or competing occupational and caregiving responsibilities [76].

Taken together, these barriers highlight an important distinction between the efficacy of exercise observed under controlled trial conditions and its sustainability in routine clinical practice, and they may help explain why individuals with FM tend to exhibit lower adherence to exercise compared to people with other chronic conditions [77].

Supporting Exercise Adherence in FM

In response to these challenges, home-based exercise has been proposed as a means to reduce logistical burdens and accommodate fluctuating symptoms, thereby supporting adherence [78–80]. However, evidence for home-based exercise in FM remains mixed, with heterogeneous interventions and variable effects across outcome domains [81]. Patients with FM often report feeling stigmatised or not taken seriously by healthcare professionals, which can undermine engagement with care [27,82,83]. In this context, a strong clinician-patient alliance is associated with better adherence [84]. In line with this, adherence to home-based exercise tends to be higher when patients feel comfortable with their therapist, receive clear information and guidance, and sense that their concerns are acknowledged [84]. These features align with self-efficacy, which is a strong predictor of adherence to home-based programmes [84]. Taken together, the key implication is that home-based exercise is more likely to be sustained when accompanied by ongoing, accessible support and communication.

Beyond the clinic, digital support offers a potential means of supporting adherence to home-based exercise outside supervised settings. Digital tools,

including mHealth applications, have been used in other clinical contexts to support home-based exercise by providing monitoring functions and patient-clinician communication [85]. However, whether such tools improve adherence or clinical outcomes in FM remains unclear.

Taken together, the central question becomes how to deliver exercise in a manner that is both feasible and maintainable in FM. A clear gap persists between current exercise guidelines, which typically recommend moderate-to-vigorous intensity training [68], and the capacity of many individuals with FM to adhere to such programmes. These challenges provide the rationale for focusing on feasible low-impact exercise modalities, which are discussed next.

Feasible Low-Impact Exercise Modalities

Although the term is not uniformly defined, ‘low-impact exercise’ is used here to denote low-intensity, brief activity. Rather than targeting traditional training thresholds (i.e., aerobic, metabolic or strength), these approaches prioritise tolerability and feasibility in daily life. In this context, low-impact exercise can be delivered as structured exercise (e.g., stretching, yoga, Tai Chi, or Pilates) or as purposeful low-intensity daily activity (e.g., walking or gardening), provided that the intensity and duration are adapted to the individual's capacity.

Current evidence suggests potential symptom benefits and generally good tolerability, with few adverse events reported in trials, although evidence remains limited [86]. Low-impact exercise modalities may be especially suitable for patients who are otherwise exercise-intolerant, as they are perceived to carry a lower risk of symptom exacerbation [29].

For many patients with FM, fluctuations in symptoms and energy levels result in substantial differences in what is achievable on “good” versus “bad” days [87]. Given their lower perceived risk of symptom exacerbation, low-impact exercise modalities may, in theory, enable patients to remain active despite symptom fluctuations. From a practical, long-term perspective, interventions for FM also need to be simple, time-efficient, and compatible with fluctuations in symptoms [74]. In this context, home-based exercise programmes may allow patients to fit exercise into their individual schedules, enabling them to engage in physical activity at times that best suit their needs.

Nonetheless, the evidence base for low-impact, home-based exercise in FM is limited, and its efficacy remains unestablished. Within this context, stretching exercises are a pragmatic low-impact modality because they are simple, low-cost, and can easily be integrated into daily routines in a home-based format [88]. Beyond these practical advantages, stretching is also assumed to have relevant mechanistic effects in FM [89–91]. These potential mechanisms, and their implications for stretching as a low-impact intervention, are considered in the following section.

Stretching: Concept and Mechanisms

Although the term "stretching" is not uniformly defined, it is often understood as *"movement applied by an internal and/or external force to elongate muscles and periarticular soft tissues, with the primary aim of increasing muscle flexibility and/or joint range of motion"* [92]. Importantly, stretching effectiveness appears to be dose-dependent, with intensity, duration, frequency, and technique influencing outcomes [93,94]. In this context, the American College of Sports Medicine (ACSM) provides a pragmatic reference standard for prescribing stretching to improve effectiveness, recommending static stretching at least 2–3 times per week, with daily practice described as most effective, performed to the point of tightness or slight discomfort, and held for 10–30 seconds for 2–4 repetitions [95]. However, how stretching is delivered and dosed varies markedly across interventions [10,60].

Stretching exercises have been widely incorporated into FM management to maintain flexibility [10]. However, beyond its traditional role in maintaining flexibility, emerging evidence suggests that stretching may also have therapeutic benefits, reducing pain and improving quality of life [96]. Yet, the clinical evidence remains inconsistent, with studies reporting mixed effects of stretching on FM symptoms [10,60]. Given inconsistent clinical findings, a structured synthesis of stretching trials is needed.

Stretching has been proposed to induce several mechanistic effects that may be particularly relevant in the context of FM [89–91]. In the following paragraphs, these proposed effects are considered in relation to pain-modulatory pathways and autonomic regulation, with particular attention to whether they can be engaged through low-impact stretching.

FM is thought to involve a shift in descending pain modulation towards net facilitation and diminished inhibitory control, thereby supporting the development and maintenance of persistent pain [30,32]. In healthy individuals, stretching can activate descending analgesic systems, including noradrenergic and endogenous opioid pathways, resulting in regional and widespread reductions in pain sensitivity [89,97,98]. This provides a plausible mechanistic rationale for investigating stretching interventions in FM, where descending inhibition is often reduced.

Current evidence for stretch-induced hypoalgesia (SIH) is derived mainly from acute, single-session studies in healthy adults [89,97,98]. It therefore remains unclear whether SIH is purely transient or whether it accumulates with repeated exposure to produce more enduring changes in pain sensitivity. This is particularly relevant in FM, where durable symptom relief is required for clinical benefit. Clarifying whether repeated stretching produces sustained changes is therefore important for judging its potential clinical relevance in FM.

Beyond the temporal aspects, stretching intensity may also be a key determinant of analgesic effects. Endogenous modulation of somatosensory input is considered a saturable phenomenon, implying that descending inhibitory systems may reach a ceiling beyond which additional noxious or more intense stimulation does not further increase analgesia [99]. Consistent with this, evidence indicates that stimulus intensity is a primary determinant of inhibitory magnitude in related paradigms, including EIH and conditioned pain modulation, with higher-intensity exercise and conditioning stimuli typically eliciting more pronounced inhibitory responses [100,101]. It is therefore plausible that SIH also depends on stretching intensity, such that higher-intensity stretching elicits larger changes in pain sensitivity than lower-intensity stretching. However, the intensity dependence of SIH has not been systematically examined.

In addition to effects on descending pain pathways, stretching may influence autonomic regulation in ways relevant to pain modulation [91]. Studies report reductions in sympathetic activity and increases in parasympathetic activity following stretching [102,103]. These autonomic changes may interact with central pain processing and facilitate engagement of descending inhibitory mechanisms, potentially enhancing the efficiency of descending pain modulation [104].

In summary, stretching may engage pain-modulatory and autonomic mechanisms relevant to FM. However, the extent to which these translate into consistent clinical benefits remains unclear. The next section, therefore, appraises the existing clinical trial evidence on stretching in FM.

Current clinical evidence on stretching in FM

Clinical trials investigating stretching in FM are generally small and most often embed stretching within broader exercise or multimodal rehabilitation programmes, with relatively few evaluating stretching as a stand-alone intervention [10]. Where studied, stretching has been compared with other exercise modalities or usual care, using outcomes spanning pain, global impact, function, and psychological variables [10,60]. However, across studies, interventions are heterogeneous and often poorly described, with substantial variation in technique, intensity, frequency, session duration, and follow-up, as well as the core outcomes used [10,60].

Although several studies report improvements in pain, physical function, and health-related quality of life, findings across trials are inconsistent, likely reflecting methodological diversity and incomplete reporting of interventions [10,60]. As a result of this heterogeneity, it is not currently possible to derive precise, evidence-based recommendations for stretching prescription in FM, including dose, intensity, and frequency [10]. This limits clinical translation because clinicians lack guidance on how to deliver stretching in practice.

From Mechanistic Studies to Clinical Trial: Rationale for the Five-Study Thesis Design

Current evidence supports stretching as a low-burden intervention with plausible pain-modulatory mechanisms relevant to FM. However, the conditions under which it might be effective, tolerable, and clinically relevant remain uncertain. Against this background, the thesis follows a staged sequence from mechanistic studies to clinical evaluation. The initial mechanistic focus was intended to determine whether stretching reliably alters pain sensitivity and whether effects are time- and intensity-dependent. This was necessary to inform the development and subsequent clinical testing of a home-based stretching protocol in FM.

Aims and hypothesis

The overall aim of this PhD was to develop and evaluate a mechanistically grounded, clinically feasible, low-intensity, high-frequency home-based stretching intervention for FM. Following a staged progression from mechanistic experiments to clinical evaluation, Studies I–V collectively aimed to develop, refine, and evaluate the clinical efficacy of a home-based stretching intervention for individuals with FM. The goal was for the intervention to be tolerable and sustainable, while maintaining sufficient dose and specificity to achieve clinically meaningful improvements in FM-related symptoms.

The overall objective is therefore operationalised through the following study-specific aims and hypotheses (Studies I–V).

Study I

Aim: To investigate the effect of six weeks of regular stretching on regional and widespread pain sensitivity and range of motion, and to examine the effect of subsequent stretching cessation on these outcomes in healthy adults.

Hypothesis: We hypothesised that regular stretching would increase pressure pain thresholds both locally and at a distant site, improve range of motion, and that these effects would abate following the cessation of the stretching period.

Study II

Aim: To summarise the efficacy of stretching exercises alone, compared with other exercise modalities or no-intervention/usual-care controls, on FM symptoms, and to describe the content of stretching interventions and the methodological quality of the current evidence.

Study III

Aim: To examine the dose-response relationship between stretching intensity and the analgesic effect on local and widespread pain sensitivity in healthy adults.

Hypothesis: A dose-response relationship was hypothesised between local and widespread pain sensitivity and stretching intensity.

Study IV

Aim: To investigate the feasibility and acceptability of a six-week home-based stretching programme in people with FM, and to explore preliminary changes in symptoms.

Hypothesis: No formal hypothesis testing was planned as the study was designed to generate feasibility and acceptability data to inform a subsequent clinical trial.

Study V

Aim: To investigate the clinical efficacy of a novel six-week, home-based stretching intervention compared with usual care in patients with FM.

Hypothesis: The six-week home-based stretching intervention was hypothesised to yield greater improvement in fibromyalgia symptoms than usual care.

Chapter 2. Methods

This thesis comprises five studies that employ different designs, with full methodological details reported in articles I–V (Appendix A-E). This chapter, therefore, focuses on the core outcome measures and methods that recur across studies. It also outlines how these were operationalised in each study (Table 1).

Summary of core methods used across studies

Pressure pain thresholds

Pressure pain thresholds (PPTs) were used as the primary outcome in Studies I and III and as a secondary outcome in Studies IV and V to assess mechanical pain sensitivity. PPT assessment is a validated technique for pain sensitivity assessment and is widely used [105,106]. It provides a standardised, quantitative measure of pain sensitivity that is conceptually aligned with nociplastic pain presentations in FM [107]. PPTs have demonstrated excellent intra- and inter-rater reliability when standardised procedures are applied [108–110], with a minimal detectable difference of approximately 15% [108,111].

PPTs were assessed using a handheld digital pressure algometer (Algometer Type 2, SBMEDIC, Hörby, Sweden) with a 1 cm^2 probe. Pressure was applied perpendicular to the tissue and maintained at a constant rate of 30 kPa/s. The first time the sensation of pressure was perceived as pain, the subject pressed a button that stopped the stimulation. The pressure value at that time point was defined as the PPT. PPTs were assessed three times at two sites in an alternating sequence, with a minimum of 20 seconds' rest between assessments to minimise the risk of pain summation [112]. Given that the PPT assessment may be susceptible to habituation effects [112,113], participants were familiarised with the procedure through assessments of PPTs at a site not used for outcome measurement prior to baseline testing.

Pain perception is considered multidimensional [105,106,114]. Consequently, quantitative assessment of pain sensitivity using a single modality of standardised stimulation is unlikely to capture the full

complexity of pain perception [105,106]. Nevertheless, PPT assessment offers a pragmatic balance between mechanistic relevance and feasibility compared to a more extensive quantitative sensory testing battery, and it is therefore widely used in both experimental and clinical pain research [105,106].

In this thesis, PPTs served two purposes: first, to assess changes in pain sensitivity over time in response to the stretching interventions (Studies I, III, IV and V); and second, to support the interpretation of whether any observed changes in pain sensitivity were predominantly regional or widespread (Studies I and III), consistent with altered local or central pain modulation. Throughout the thesis, PPTs were assessed at two sites, with site selection aligned with the study aims. Studies I and III used the right m. tibialis anterior and the left middle deltoid to compare regional versus widespread changes. In contrast, Studies IV and V used the right m. tibialis anterior and left upper trapezius without attempting to differentiate local from more widespread effects.

It is essential to recognise that PPTs do not directly assess segmental or central pain inhibition [115]. Rather, PPTs provide an interpretable threshold that is consistent with changes in pain processing and/or pain tolerance and must therefore be interpreted within the broader mechanistic context of this thesis. Moreover, pain is, by definition, a multidimensional personal experience [116], and objective findings may not always translate directly to real-world pain experience or clinical practice [117]. Accordingly, PPT findings were considered alongside patient-reported outcome measures to capture the broader impact of symptoms and their clinical relevance (studies IV and V).

The Revised Fibromyalgia Impact Questionnaire

The Revised Fibromyalgia Impact Questionnaire (FIQ-R) was used as the primary outcome in Study V and as a secondary outcome in Study IV to quantify disease burden and its impact on functional ability and social participation in patients with FM. The FIQ-R is the most widely used FM-specific measure to assess the full spectrum of FM-related problems and response to therapy [118]. The FIQ-R comprises 21 items across three

domains: function (9 items), overall impact (2 items), and symptoms (10 items). Each item is scored from 0 to 10, with lower scores indicating less impairment or greater improvement. Domain scores are calculated by summing item scores and applying the standard scaling factors (function ÷ 3, overall impact ÷ 1, symptoms ÷ 2), yielding domain ranges of 0–30 for function, 0–20 for overall impact, and 0–50 for symptoms. The FIQ-R total score (0–100) is the sum of the three domain scores, with higher scores indicating greater FM-related impact [119]. The FIQ-R demonstrates good reliability and validity, with sound psychometric properties [118–121]. Evidence also indicates that the FIQ-R performs comparably across sex, ethnicity, and education groups, supporting its use across these demographic strata [121].

The minimal clinically important difference (MCID) for the FIQ-R total score has not yet been firmly established. Although the FIQ-R was developed as an updated version of the original FIQ, it differs slightly in item content and scoring structure [119]. In practice, many studies therefore reference the MCID derived for the original FIQ total score (14%) when interpreting change in the FIQ-R total score [122–124]. Reports of a strong correlation between FIQ and FIQ-R scores support this [119], suggesting broadly similar response patterns across the two instruments. Nevertheless, given differences between the measures, applying the FIQ-derived threshold to the FIQ-R should be regarded as provisional [125]. Accordingly, in this thesis, the change in overall FM impact was interpreted using the 14% benchmark alongside effect sizes and findings across secondary outcome measures (studies IV and V).

Health-related quality of life

Health-related quality of life (HRQL) was assessed as a secondary outcome in Studies IV and V using the Short Form-36 (SF-36) to capture perceived physical and mental health status. It was selected because it provides a multidimensional profile of perceived health that extends beyond pain intensity, including domains commonly affected in FM, such as physical functioning, vitality, and mental health, and is commonly evaluated in FM intervention research [10,58].

The instrument comprises eight domains: physical functioning, role limitations due to physical problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Scores are transformed to a 0–100 scale, with higher scores indicating better perceived health status [126]. Domain scores were summarised using the Physical Component Summary (PCS) and Mental Component Summary (MCS), which are generally considered acceptable summary indices of physical and mental health status [127]. PCS and MCS were used to support the interpretation of whether changes were predominantly physical, psychological, or both, a clinically relevant distinction in FM given its multidimensional symptom profile. The SF-36 has demonstrated acceptable reliability and validity across clinical and population-based samples [127,128]. To interpret change, estimated MCID ranges have been reported for the component scores. Accordingly, in this thesis, changes in PCS and MCS were interpreted in relation to MCID estimates of 2.62–4.69 points for PCS and 4.46–6.79 points for MCS, alongside effect sizes and patterns across other outcomes [128,129].

Range of motion

Passive knee extension range of motion (ROM) was assessed as a secondary outcome in Studies I, III, IV, and V to quantify knee extension flexibility under a standardised passive end-range criterion, using the Biodex System 4 Pro isokinetic dynamometer. The Biodex is widely regarded as a gold-standard approach for objective ROM assessment and demonstrates excellent reliability and validity when standardised procedures are applied [90,130,131]. Based on the standard error of measurement (SEM) reported by Drouin et al., the minimum detectable change (MDC) at the 95% confidence level is 1.2 degrees [130]. However, while the MDC provides an estimate of measurement precision, there is no consensus on the minimal clinically relevant change in passive knee extension ROM assessed with an isokinetic dynamometer. For context, the International Knee Documentation Committee (IKDC) criteria define normal knee extension as being within 2 degrees of the contralateral knee, providing a reference benchmark for interpreting the findings [132].

ROM assessments followed a standardised passive knee extension protocol. Participants were seated and secured in the chair with their hips positioned at 100° flexion and their knees at 90° flexion. The dynamometer lever arm passively extended the knee at an angular velocity of 5°/s [90]. The combined trunk and hip position was used to place tension primarily on the knee flexor muscle-tendon units and to minimise compensatory movement during testing [133]. Participants were instructed to stop the lever arm by pressing a stop button when the sensation changed from stretch to pain. ROM was operationalised as the maximal joint angle achieved at this pre-defined end-range criterion.

Self-reported physical activity

Self-reported physical activity was assessed as a secondary outcome measure in Studies I, IV, and V to characterise habitual activity over the preceding seven days. Habitual activity was considered relevant because baseline activity levels are associated with symptom severity and pain intensity in FM [134,135], and because changes in activity during the intervention period could plausibly contribute to changes in pain sensitivity, physical function, and health-related quality of life [135,136].

Physical activity was measured using the International Physical Activity Questionnaire (IPAQ) short form [137], a recommended and widely used self-report instrument for estimating physical activity in research and clinical populations [138]. The IPAQ short form is a 9-item questionnaire capturing perceived time spent in vigorous-intensity activity, moderate-intensity activity, walking, and sitting over the previous seven days [137]. Scores were calculated according to standard IPAQ scoring procedures and expressed as metabolic equivalent minutes per week (MET-min/week). The IPAQ short form has demonstrated acceptable reliability and validity [138].

Self-reported physical activity is, however, susceptible to recall bias [138,139] and social desirability effects [140], and may not correspond closely to objectively measured activity [141,142]. Accordingly, in this thesis, IPAQ findings were interpreted as perceived activity levels and contextualised alongside other outcomes, rather than treated as a precise estimate of physical activity.

Mobile health application support

Studies I, IV, and V used a mobile health (mHealth) application to support adherence to home-based stretching and to standardise intervention delivery. The applications were used to enable prospective session logging, provide video-based exercise instruction, and enable participant-investigator messaging for timely clarification of questions related to the intervention and maintain ongoing contact during the intervention periods. Platform details and study-specific procedures are provided in the methods sections of the published papers. Studies I and IV used DigiFys (My Physiotherapist, Viborg, Denmark), while Study V used DigiFys and ExorLive Go (ExorLive AS, Oslo, Norway). Both platforms provided similar core functions.

Table 1. Overview of Studies I–V

Study	Design	Population (N)	Setting	intervention	Outcome measures
I	Experimental longitudinal study	Healthy adults (N = 26)	Laboratory assessments; home stretching	Daily bilateral static knee-flexor stretch to a stretching sensation (discomfort). Dose: 2×30 s; rest ≥30 s; 2 min/day for 6 weeks.	Primary: PPTs Secondary: ROM (Biodex), IPAQ.
II	Systematic review	9 RCTs in fibromyalgia. Total N=497	Outpatient clinics and laboratory	Stretching-only interventions in FM (as reported in included trials).	Efficacy on FM symptoms; intervention content/prescription; methodological quality.
III	Randomised crossover study	Healthy adults (N = 31)	Laboratory	Two unilateral right knee-flexor static stretching sessions: (1) stretching sensation; (2) first onset of pain. Each: 4×30 s bouts; 30 s rest.	Primary: PPTs (local vs widespread; intensity response). Secondary: ROM (Biodex)
IV	Prospective pre–post feasibility study	Fibromyalgia (N = 12)	Laboratory assessments; home stretching	Daily bilateral static stretching (knee flexors, hip abductors, shoulder elevators) to a stretching sensation. Dose: 2×30 s per stretch; rest ≥30 s; 6 min/day for 6 weeks.	Primary: feasibility and acceptability; (online focus group). Secondary: FIQ-R, PPTs, ROM, SF-36, IPAQ and adherence.
V	Randomised controlled trial (waitlist control; 1:1 allocation)	Fibromyalgia (N = 58)	Laboratory assessments; home stretching	Home-based static stretching as in Study IV; 6 min/day for 6 weeks;	Primary: FIQ-R. Secondary: PPTs, ROM, SF-36, IPAQ, adherence (app log).

Note. mHealth app support was utilised in Studies I, IV, and V. DigiFys was used in Studies I, IV, and V, while ExorLive Go was also used in Study V.

Summary of Thesis Papers

The following sections provide brief summaries of the methods for Studies I through V. These summaries aim to provide an overview of the design and key methodological decisions underlying each study, while detailed descriptions are reported in the original articles. The full versions of articles I–V are included in Appendices A–E.

Study I. The effect of six-week regular stretching exercises on regional and distant pain sensitivity: an experimental longitudinal study on healthy adults [143]

Methods

A single-group repeated-measures design was used, with a six-week intervention followed by a four-week cessation period. Assessments were conducted at baseline, after six weeks, and after ten weeks.

Participants

Healthy adults aged 18–65 years who were naïve to experimental pain testing were eligible.

Intervention

Participants completed six weeks of daily bilateral static stretching of the knee flexors. Stretching was performed to the point of discomfort, defined as a clear stretch sensation. Each stretch was held for 30 seconds and repeated twice, with at least 30 seconds of rest between bouts. Participants were asked to maintain usual activity levels and avoid additional flexibility exercises during the study period. An mHealth application (DigiFys) provided video instruction and exercise logging, and the investigator contacted participants via the app every fortnight.

Outcomes

The primary outcome was pain sensitivity, assessed by PPTs at a regional site (right tibialis anterior) and a distant site (left middle deltoid). Secondary outcomes included passive knee extension ROM.

Sample size

The sample size was determined a priori to detect a minimal meaningful change of 20% in the primary outcome (PPTs). A priori power analysis indicated that 26 participants were required to detect a 20% change in PPTs with 90% power ($\alpha = 0.05$), allowing for 20% loss to follow-up.

Statistical analysis

Time effects on PPTs and range of motion were analysed using one-way repeated-measures ANOVA with Bonferroni-adjusted post hoc comparisons. Relative change scores were calculated to describe changes over time. Associations between changes at regional and distant pressure sites were examined using Spearman's correlation. Effect sizes were reported as partial eta-squared, and missing values were handled using the last observation carried forward method when loss to follow-up occurred.

Study II. The effectiveness of stretching exercises in patients with fibromyalgia: A systematic review [144]

Methods

The systematic review was conducted in accordance with PRISMA guidelines and prospectively registered in PROSPERO (CRD42023399614).

Eligibility criteria

Eligibility criteria were defined using PICOS. Studies were required to include adults with FM diagnosed according to prevailing ACR criteria and to evaluate stretching as a stand-alone intervention (e.g., static, dynamic, or PNF-inspired) compared with other exercise modalities, usual care, or untreated controls. Multimodal interventions combining stretching with other exercise components were excluded.

Search strategy and study selection

Searches were conducted from inception to 12 April 2023 and updated on 29 March 2024 across MEDLINE, PubMed, CINAHL, Web of Science, SCOPUS, AMED, PEDro, ClinicalTrials.gov, and the Cochrane Trials Register. Two reviewers independently screened titles/abstracts and full texts

(MPS & AMLD). Disagreements were resolved by consensus or third-party arbitration (AR).

Data extraction and synthesis methods

One reviewer extracted data (MPS) and a second reviewer validated the extraction against the original reports (AR).

Outcomes and synthesis approach

Pain intensity was specified as the primary outcome. Intervention protocols were additionally characterised by key stretching prescription parameters (type, intensity instructions, frequency, duration, and repetitions). Secondary outcomes were self-reported quality of life, fatigue, physical functioning and physical and mental health scores.

Risk of bias and certainty of evidence assessment

Risk of bias was assessed using the Cochrane Risk of Bias tool (RoB 2), and the certainty of evidence was evaluated using GRADE by two reviewers (MPS & AMLD), with adjudication through discussion.

Study III. The effect of stretching intensity on pain sensitivity: A randomized crossover study on healthy adults [145]

Methods

A randomised, repeated-measures crossover design was used with two experimental sessions separated by a washout period of at least 24 hours.

Participants

Healthy adults aged 18–55 years were recruited. Participants were instructed to refrain from physical exercise on experimental days.

Intervention

Participants attended the laboratory on two occasions and completed unilateral static stretching of the right knee flexors under two intensity conditions: (1) stretching to the point of stretch (first sensation of

stretching/discomfort) and (2) stretching to the first onset of pain. In each session, stretching comprised four 30-second bouts separated by 30 seconds of rest, delivered in a standardised seated position using an isokinetic dynamometer (Biodex).

Outcomes

The primary outcome measure was pain sensitivity expressed as regional (local) and distant (widespread) PPTs. Mean values were used for analysis, and participants were blinded to the recorded thresholds. Passive knee extension ROM was assessed as a secondary outcome.

Sample size

An a priori power analysis indicated that 31 participants were required to detect a 15% between-condition difference in PPT with 90% power (α = 0.05), allowing for 20% attrition.

Randomisation

Session order (pain first vs stretch first) was randomised a priori using counterbalanced block randomisation (1:1, blocks of four) generated by the investigator (MPS). Allocation concealment was maintained using sealed opaque envelopes, handled only by the two experimenters (LØH and KKE), who enrolled participants and assigned session order. The experimenters (LØH and KKE) collected all outcome measures. Participants were blinded to PPT results, and both participants and experimenters were blinded to ROM values. The investigator (MPS), blinded to allocation and outcome values, conducted the statistical analyses and interpretation.

Statistical analysis

Time (pre vs post) × intensity (stretch sensation vs first onset of pain) effects were analysed using two-way repeated-measures ANOVA, with session order included to evaluate potential order effects. Significant effects were examined with Bonferroni-corrected paired post hoc comparisons, and effect sizes were reported as partial eta-squared. Relative PPT changes between intensity conditions and associations across intensities were examined using non-parametric tests (Wilcoxon) and Spearman correlations, respectively.

Study IV. Exploring the feasibility, acceptability and preliminary efficacy of a Home-Based stretching program for adults with fibromyalgia: a prospective Pre-Post feasibility study [146]

Methods

This prospective feasibility study used a pre-post design, supplemented with online focus group interviews, to evaluate the feasibility, acceptability, and preliminary efficacy of a six-week home-based low-impact, high-frequency stretching intervention in individuals with FM.

Participants

Adults aged 18–55 years with FM diagnosed according to ACR criteria were eligible. Participants were recruited via the Danish Fibromyalgia & Pain Association (North Denmark Region) and social media.

Intervention

Participants completed six weeks of daily static stretching, comprising two 30-second bilateral bouts targeting the knee flexors, hip abductors, and shoulder elevators, with at least 30 seconds' rest between bouts. Stretches were performed until a stretching sensation was felt. Instructions were provided face-to-face by a physiotherapist (MPS) and reinforced via the DigiFys app. Participants logged completed sessions in the app, and the principal investigator (MPS) contacted participants weekly via the app to monitor responses and provide feedback. Participants were encouraged to maintain their usual routines and avoid changing their medication or initiating new exercise regimens during the study period.

Outcomes

The primary outcome was the participants' experiences of the intervention, assessed after completion of the six-week programme using semi-structured online focus group interviews conducted via Microsoft Teams and facilitated by an independent researcher. Secondary outcomes (at baseline and 6 weeks) included the FIQ-R, SF-36, PPTs, ROM, and IPAQ, along with self-reported adherence.

Sample size

The study was not powered to detect definitive clinical effects. A pragmatic target sample of 12 participants was specified for the feasibility assessment.

Qualitative analysis

The qualitative analysis followed an inductive thematic approach based on Braun and Clarke's six-step framework. Interviews were transcribed semi-verbatim, anonymised, and inductively coded in NVivo 14 (MPS). Codes were iteratively organised into themes and sub-themes. Two researchers (MPS and LLL) reviewed and refined the coding and theme structure until consensus was reached, and AR reviewed the final themes. Illustrative quotes were extracted and translated into English to support the narrative interpretation.

Patient involvement

The protocol was reviewed by Aalborg University's Centre for General Practice user panel (21 September 2023), which informed refinements to participant information and the perceived burden of the intervention.

Statistical analysis

Pre-post differences were examined using Wilcoxon signed-rank tests. An intention-to-treat approach was applied, with baseline values carried forward for missing post-intervention data.

Study V. Efficacy of a novel home-based stretching program on fibromyalgia symptoms: a randomised controlled trial [147]

Methods

Study design

This two-arm, parallel-group, superiority randomised controlled trial with a waitlist control evaluated a six-week low-impact, high-frequency home-based stretching intervention for adults with FM (October 24, 2024, to May 22, 2025). The trial protocol has been published and was reviewed by Aalborg University's Centre for General Practice user panel and the regional practice network. Findings from a preceding feasibility study informed refinements to the intervention, participant materials, and the planned sample size.

Eligibility criteria

Adults aged 18–65 years with fibromyalgia diagnosed according to the 2016 ACR criteria were eligible for inclusion.

Randomisation and masking

Participants were randomly allocated in a 1:1 ratio to the stretching intervention or wait-list control using sex-stratified, counterbalanced block randomisation (block sizes 4-8). Allocation was concealed using sealed, opaque envelopes. Participants and the investigator (MPS) were not blinded to group allocation. However, the outcome assessor (MPS) remained blinded to all patient-reported outcomes, and participants were not given access to their baseline questionnaire responses or objective measurement results.

Interventions

The intervention group completed a six-week home-based static stretching programme (6 minutes/day) in addition to usual care. Each session comprised two 30-second bouts of bilateral stretches targeting the knee flexors, hip abductors, and shoulder elevators, with at least 30 seconds' rest between bouts. Participants were instructed to apply tension until a stretching sensation was felt. The exercise sequence was flexible, and minor individual adjustments were permitted. Delivery, adherence logging, and participant-researcher communication were supported via an mHealth application, and participants were contacted approximately weekly. Participants were asked to maintain their usual routines and avoid changing their medication or starting new exercise routines during the study.

The control group received usual care and were instructed to maintain their usual routines, refrain from initiating new exercise regimens or stretching exercises independently, and avoid changing their medication during the study period. After completing the follow-up assessments, participants in the control group were offered the stretching intervention. To support retention and monitoring, MPS maintained contact with each participant approximately weekly via email.

Outcomes

Assessments were conducted at baseline and after six weeks [148]. Baseline data included demographics, clinical history, and current medication. The primary outcome was the FIQ-R total score. Secondary outcomes included

SF-36 (PCS and MCS), habitual physical activity (IPAQ), knee-extension ROM, and PPTs (tibialis anterior and upper trapezius), and FIQ-R pain and stiffness subscores.

Adherence and harms

Adherence was assessed via app-based exercise logs. Harms were monitored through app-based self-reports (e.g., soreness, pain exacerbation, injury).

Statistical analysis

Sample size was informed by feasibility data. Assuming no change in the control group and a minimal clinically relevant improvement of 14% in the intervention group ($\alpha = 0.05$, power = 0.90), 24 participants were required per group. Allowing for a 20% loss to follow-up, the target sample size was 58.

The primary analysis used an intention-to-treat approach with baseline observation carried forward for missing data. Sensitivity analyses compared intention-to-treat results with a predefined per-protocol analysis (≥70% adherence, complete primary outcome data, and no major protocol violations). No interim analyses were conducted. Group × time effects were examined using two-way mixed ANOVA with Bonferroni-adjusted post hoc tests; effect sizes were reported as partial eta-squared ($\alpha = 0.05$).

Chapter 3. Results and Discussion

The results and discussions are presented study by study. For each of the five studies, the section follows the same two-part structure: first, a brief summary of the key results and their interpretation as reported in the corresponding article; second, an extended discussion that goes beyond the published article, informed by a structured critical appraisal using a tool aligned to the study design. The full versions of articles I–V are included in Appendices A–E of this PhD thesis.

Study I. The effect of six-week regular stretching exercises on regional and distant pain sensitivity: an experimental longitudinal study on healthy adults [143]

One participant withdrew for reasons unrelated to the study; 26 participants completed follow-up. Mean adherence to the six-week stretching programme was 87.2% ± 10.2%.

From baseline to post-stretch, PPTs increased significantly at both the regional site (tibialis anterior; +36.7%, p=0.003) and the distant site (deltoid; +18.7%, p=0.042), and passive knee-extension ROM increased significantly (+3.6%, p=0.002). (Table 2)

No statistically significant changes were observed from post-stretch to post-cessation for PPTs or ROM (all p=1.000), indicating maintenance over the cessation period.

From baseline to post-cessation, PPTs remained significantly higher at the tibialis anterior (+41.2%, p=0.001), whereas the deltoid change was not statistically significant (+15.4%, p=0.127). ROM remained significantly increased (+3.6%, p=0.005).

Relative changes in regional and distant PPTs were positively correlated from baseline to post-stretch (ρ=0.479, p=0.015) and from post-stretch to post-cessation (ρ=0.597, p=0.002).

Table 2. Absolute values (means (SD) and 95% CI) for ROM and PPTs. (Adapted from study 1, Appendix A)

	Baseline	**Six weeks (Post-stretch)**	**Ten weeks (Post-cessation)**
Range of motion (deg.)	172.5 ± 10.1 (168.3-176.8)	178.7 ± 11.9 (173.9-183.9)*	178.5 ± 10.2 (174.5-183)¤ #
Pressure Pain Thresholds (Kpa) Tibialis Anterior	304.6 ± 136.6 (249.3-359.7)	391.1 ± 132.3 (337.7-444.6)*	412 ± 174 (341.8-482.4)¤ #
Pressure Pain Thresholds (Kpa) Deltoid	263.6 ± 122.3 (214.2-312)	307.6 ± 161.9 (242.2-373)*	301.1 ± 166.2 (233.9-368.2) ¤

Legend: * = significant difference between baseline- and post-stretch, ¤ = significant difference between post-stretch and post-cessation, and # = significant difference between baseline and post-cessation, mean (SD).*

The main findings showed that regional and widespread pain sensitivity decreased after 6 weeks of regular stretching. However, the hypoalgesic effect of regular stretching did not abate after 4 weeks of cessation.

The hypoalgesic effect seen in the present study occurred with multisegmental manifestations; hence, the present findings align with current evidence suggesting that the hypoalgesic effect of stretching exercises may be related to endogenous inhibitory pain mechanisms [89,98]. The regional response appeared more pronounced than the widespread response. Further work is needed to establish whether there is a difference in the magnitude of the regional and widespread analgesic response to stretching.

Current evidence suggests that the durational effect of stretching exercises is related to regular modifications of somatosensory input (i.e., the frequency of stretching exercises) [149,150]. However, the present results raise questions about the current understanding of the long-standing effect of stretching exercises on pain sensitivity; hence, further research on the long-term hypoalgesic effect of stretching exercises in both healthy and patient populations is warranted.

The lack of a control group is a limitation, as it prevents comparison with natural time-course changes and limits the ability to quantify inherent outcome variability, including possible learning effects from repeated testing. Controlled studies are therefore needed to quantify effects relative to no-

treatment comparators. Because the study included only healthy participants, it is uncertain whether the observed hypoalgesic effects would generalise to individuals experiencing clinical pain. This should be examined in clinical pain populations.

Due to COVID-19 restrictions at the time of enrolment, participants were recruited mainly from the University College of Northern Denmark, resulting in a young sample (21–30 years). However, evidence suggests that stretching effects do not depend on age [151] or sex [98], so the convenience sampling likely had limited influence on the findings.

Extended discussion

The following discussion points are, in part, informed by a structured critical appraisal of Study I using the Cochrane Collaboration ROBINS-I V2 assessment tool for non-randomised studies of interventions [152].

Study I advances the evidence base on SIH by demonstrating longitudinal change in PPTs with repeated stretching, including partial retention after cessation. This addresses a gap in the literature, which is dominated by acute paradigms [89,97,98,143], and is directly relevant to durability. By indicating that the hypoalgesic effects may persist beyond the acute effects typically described, the retention finding warrants confirmatory evaluation in larger samples and clinical populations. The findings also corroborate the established hypothesis that SIH reflects centrally mediated modulation and therefore support the current mechanistic understanding of SIH.

Habitual physical activity was assessed using the IPAQ, which shows acceptable test-retest reliability but tends to overestimate activity and demonstrates limited concordance with objective measures such as accelerometry, particularly for detecting change over time [138]. As a result, changes in habitual activity may have acted as a residual confounder for PPT outcomes [153]. This could be mitigated analytically by covariate adjustment for IPAQ or through sensitivity analyses. However, current evidence suggests that higher physical activity levels are associated with greater pressure pain tolerance [153]. Given that the results showed a decrease in habitual activity levels during the study, this may bias results

towards lower PPTs, suggesting that the observed PPT increase is unlikely to be explained by rising activity levels.

Despite the use of a standardised algometry protocol, having the same investigator design the study, collect PPTs, and conduct the analyses increases susceptibility to expectancy effects. This is relevant because PPTs are not purely objective but depend on participant judgement and examiner-dependent factors, including probe placement, pressure application rate, and verbal cues [154]. Although reliability studies show good-to-excellent intra-rater reliability for PPT, they also indicate that longitudinal change should be interpreted against measurement error (e.g., standard error of measurement and smallest/minimum detectable change) rather than statistical significance alone [108]. Accordingly, changes were interpreted using a pre-specified minimal meaningful change threshold of 20% [111]. The distant effect should therefore be interpreted with caution. Although it exceeded the generally accepted MCID (15%), the evidence supporting a true distant effect is not definitive.

The presence of multisegmental hypoalgesia with correlated regional and distant PPT changes, in the present study, is compatible with central modulation of nociceptive input, similar to EIH, which is often attributed in part to descending inhibitory pathways [100,155,156]. However, PPT correlations alone cannot determine the underlying mechanisms. EIH and conditioned pain modulation overlap but also differ in their temporal and spatial profiles, suggesting contributions from supraspinal, segmental spinal, and peripheral mechanisms [67,157]. Thus, it remains unclear whether the dominant driver behind SIH is descending inhibition, spinal gating, autonomic shifts, or a combination [157–159].

The retention of the hypoalgesic effects following cessation is noteworthy, as it suggests that stretching-associated increases in PPTs may persist beyond the period of active intervention. As a proof-of-concept study in healthy adults, the findings primarily establish plausibility rather than clinical effectiveness, and it remains uncertain whether comparable effects would be observed in FM. Nevertheless, the apparent durability of the response provides a clear rationale to proceed to confirmatory studies in individuals with FM to determine whether regular stretching can produce

sustained changes in pain sensitivity and improve clinically relevant outcomes such as quality of life and physical and mental function.

Study II. The effectiveness of stretching exercises in patients with fibromyalgia: A systematic review [144]

The searches identified 3564 records, and nine randomised trials (cumulative n = 497) were included [96,160–167]. Substantial heterogeneity in interventions, comparators, and outcome measures precluded meta-analysis; findings were therefore synthesised narratively. Across trials, stretching was typically delivered as supervised sessions (30–60 minutes) one to three times per week, and in seven of nine studies, stretching served as the comparator rather than the index intervention.

When mapped against the ACSM criteria [95], no trial delivered an intervention fully congruent with these principles, and adherence varied considerably. Consequently, key prescription parameters, particularly stretching type, intensity, and repetitions, were often incompletely reported.

Risk of bias concerns most commonly related to the randomisation process and deviations from intended interventions, alongside frequent issues with missing outcome data and outcome measurement. Overall, stretching interventions were generally associated with improvements in pain, health-related quality of life, and physical and mental functioning. However, the certainty of evidence was very low due to the risk of bias, inconsistency arising from heterogeneous prescriptions, and imprecision related to small samples and wide confidence intervals.

Study II aimed to summarise the efficacy of stretching exercises alone compared with other exercise modalities or untreated controls on FM symptoms, and to examine the content of stretching interventions and the methodological quality of the current evidence.

The major finding of the study was that stretching may improve pain, physical function, mental functioning, depression, and quality of life in adults with FM, but the certainty of evidence is low. These findings broadly align with Couto et al. [60], who reported positive effects on pain, physical functioning, and quality of life, but only modest effects on depression and the mental component of health-related quality of life. Kim et al. similarly judged the evidence to be constrained by the small number of trials and participants, as well as by unclear or high risk of bias [168].

One of the main limitations of the included trials was the marked heterogeneity of the stretching interventions and their limited alignment with the ACSM criteria [95], a concern also raised in previous reviews [60,168]. Limited alignment with ACSM criteria may indicate that some interventions were underdosed, potentially contributing to an underestimation of benefits.

Another key limitation was that stretching was mainly used as the control condition. In seven of nine trials, it served as the comparator [160–166] and was often prescribed to match the active intervention format (supervised 30–60 minute sessions, one to three times weekly). This may be problematic because stretching efficacy depends on dose parameters, including intensity, duration, and frequency [93,169]. SIH has been proposed to involve descending inhibitory mechanisms and endogenous opioid activity [91,98,143]. However, endogenous pain inhibition is likely saturable, implying a ceiling beyond which these mechanisms cannot further reduce pain [89,99]. These considerations support the rationale for shorter, more frequent stretching prescriptions when evaluating clinical benefit in FM.

Extended discussion

The following discussion points are, in part, informed by a structured critical appraisal of Study II, using the AMSTAR 2 tool to assess the methodological quality of systematic reviews [170].

Study II advances the evidence base on stretching in FM by synthesising trial findings and grading the certainty of evidence across core outcomes. It also addresses a key gap in the literature, that substantial heterogeneity in stretching prescriptions and trial methods has often not been explicitly accounted for when drawing overall conclusions [10,60]. By demonstrating very low certainty across outcomes and limited scope for meaningful pooling, the review supports the need for better-specified protocols, improved trial conduct/reporting, and usual care/no-treatment comparators to estimate absolute efficacy.

Although the review applied RoB 2 and GRADE appropriately, the interpretation was not consistently aligned with the resulting certainty ratings. All key outcomes were graded as very low certainty due to serious risk of bias, heterogeneity in intervention content, and imprecision. Nevertheless, the article concludes that stretching exercises may improve pain, health-related quality of life, and physical and mental functioning in people with FM, and could be considered as part of treatment [144]. This framing risks

encouraging unwarranted confidence in both the presence and magnitude of effects.

Consistent with AMSTAR 2 standards, further methodological limitations warrant consideration and may reduce confidence in the review's findings. The review excluded trials for combining stretching with other exercise interventions, consistent with the pre-registered exclusion criteria, but it did not provide a comprehensive table of excluded studies, along with the study-level reasons for exclusion [144]. Consequently, transparency and reproducibility remain limited, and readers cannot fully audit eligibility decisions, leaving residual risk of selection bias.

One reviewer completed data extraction with second-reviewer validation, rather than independent duplication [144], which may increase the risk of extraction errors or selective emphasis in outcome selection. While the direction of any bias is uncertain, errors could have inflated treatment effects. Independent dual extraction with consensus and third-reviewer adjudication would reduce this risk. However, data were validated against the published results and the extraction table, suggesting a low likelihood of material extraction errors.

Determining whether stretching provides meaningful benefit in FM requires trials with a usual-care/no-treatment comparator [171]. Within the included evidence, stretching was frequently used as the reference intervention, serving as the comparator in 7 of 9 trials evaluating alternative exercise modalities [144]. Consequently, the current trials are better suited to judging whether stretching is broadly comparable to alternative exercise approaches than to estimating its absolute efficacy. This risks inferring efficacy from active-versus-active comparisons, despite limited direct testing against usual care. Accordingly, the current trials represent an early stage in the evidence pathway and support well-specified trials comparing stretching with usual care/no treatment.

Study III. The effect of stretching intensity on pain sensitivity: A randomized crossover study on healthy adults [145]

Thirty-one participants (n = 24 female) were analysed (mean age 29.7 ± 10 years). The average interval between sessions was 4 ± 3 days.

Following stretching to the point of stretch, regional PPTs increased by 22.2% (93.2 kPa, p = 0.001) and distant PPTs by 15.0% (50.9 kPa, p = 0.012). Following stretching to the first onset of pain, regional PPTs increased by 20.0% (90.3 kPa, p = 0.001) and distant PPTs by 15.1% (52.1 kPa, p = 0.004) (Figures 1–2). There were no significant between-condition differences in the relative (percentage) change in regional or distant PPTs from baseline to post-stretch (all p > 0.991).

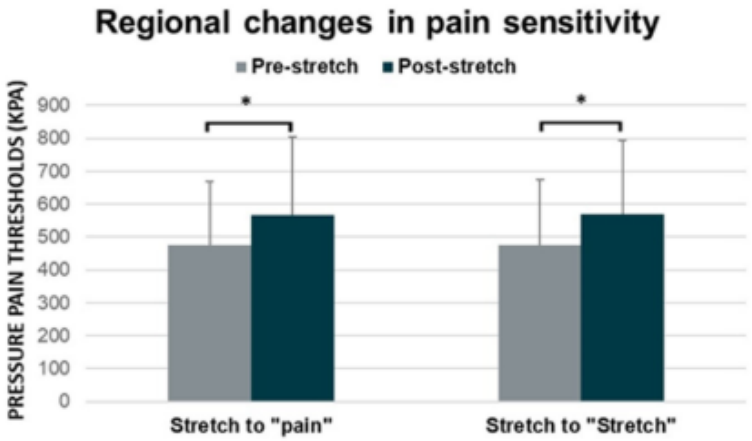

Figure 1. Pressure pain thresholds at the tibialis anterior site (regional site) were measured before (pre-stretch) and after stretching (post-stretch) to the first sensation of stretch and the first onset of pain. Data are reported as absolute mean ± SD. Significantly different compared with pre-stretch (*) (p < 0.05). (Adapted from article 3, Appendix C)

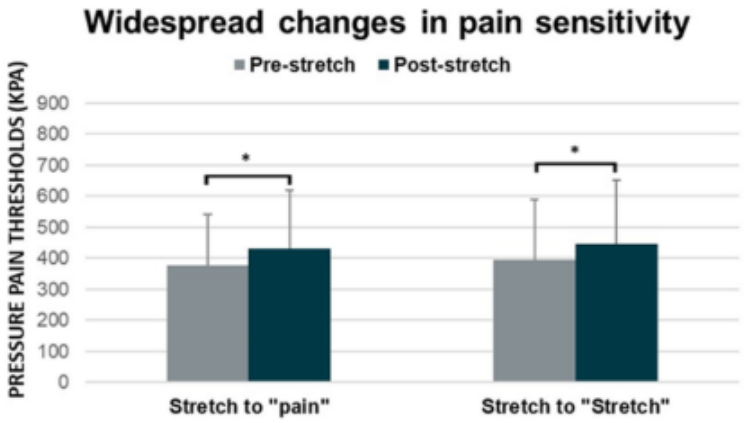

Figure 2. Pressure pain thresholds at the deltoid site (widespread site) were measured before (pre-stretch) and after stretching (post-stretch) to the first sensation of stretch and

the first onset of pain. Data are reported as absolute mean ± SD. Significantly different compared with pre-stretch (*) ($p < 0.05$). (Adapted from article 3, Appendix C)

The main findings showed a significant widespread analgesic effect following acute bouts of stretching. However, contrary to our expectations, stretching intensity did not show a dose-response relationship with the hypoalgesic effect of stretching.

These results add to the growing body of research suggesting that stretching can elicit multisegmental SIH [97,98,143]. A saturable inhibitory response may help explain the absence of an intensity effect [99]. While EIH is often intensity dependent, with larger effects at higher intensities [155,158,172], the present findings showed no intensity dependence of SIH, suggesting a lower intensity threshold for SIH than for EIH.

Although extensive research has shown the positive effects of acute and regular stretching on musculoskeletal and nociplastic pain, there is limited evidence to support the application of specific protocols for pain reduction [91]. The present findings showed a significant acute hypoalgesic effect of stretching exercises, regardless of stretching intensity. This supports the possibility that, when the aim is pain relief, stretching at a lower intensity (i.e., the sensation of stretch) may be preferable to higher intensities (i.e., the first onset of pain).

Study III assessed only the acute effects of stretching intensity on regional and distant pain sensitivity. Therefore, a dose-response relationship may still emerge with repeated stretching over time, even if such intensity effects were not evident after a single session. Because the sample comprised healthy participants, it remains uncertain whether similar acute analgesic effects of stretching would be observed in clinical pain populations, where endogenous inhibitory mechanisms are often compromised.

Extended discussion

The following discussion points are, in part, informed by a structured critical appraisal of Study 3 using the Cochrane Collaboration RoB 2 tool for randomised crossover trials [173].

Study III advances the evidence base on SIH by examining whether acute hypoalgesia is intensity-dependent. This addresses a gap in the literature, which has largely described acute SIH without clarifying whether greater perceived intensity is associated with greater hypoalgesia. By showing

comparable PPT increases across intensities despite markedly larger ROM gains at higher intensity, the findings suggest that any additional acute hypoalgesic benefit of stretching to pain onset may be limited within the examined range. The findings also support the current mechanistic understanding of SIH [97,98,143] and warrant confirmatory studies using wider intensity separation and clinical pain populations.

The findings support a mechanistic rationale for targeting a non-painful stretching intensity when the aim is to reduce pain, as higher intensities approaching pain onset did not confer additional hypoalgesia [145]. This distinction is clinically relevant in FM, where painful stimuli may reduce acceptability and adherence. However, as Study III examined an acute response in healthy adults, its mechanistic and prescription implications for FM are hypothesis-generating rather than directly generalisable. Nonetheless, the results provided a defensible mechanistic basis for selecting a non-painful stimulus intensity to carry forward into Studies IV–V.

Given that the main inference is a null dose-response, even small residual carryover effects could attenuate between-intensity differences in PPTs. Although washout adequacy was not formally tested, the mean inter-session interval of 4 ± 3 days, the absence of session-order-related interactions, and the transient nature of EIH [174,175] make any meaningful physiological carryover unlikely.

PPT assessments were conducted by the same tester across sessions, and the tester was not blinded to the intervention condition (pain vs stretch) [145], which introduces potential for differential measurement through expectancy effects or subtle variations in delivery (e.g., probe placement, rate of applied pressure, and verbal cues). However, the statistical analyses were conducted by an independent researcher blinded to allocation, which likely reduced the risk of analysis-stage bias (e.g., selective modelling or interpretive emphasis) [176,177], but this does not mitigate the potential bias introduced at the point of outcome measurement.

A critical interpretive question is whether the “no dose-response” finding reflects a true ceiling effect in SIH or, alternatively, limited contrast between conditions. If inhibitory modulation is saturable, the higher-intensity condition may not elicit materially greater PPT changes once a threshold for engaging inhibitory mechanisms is reached [99]. Conversely, null dose-response findings can arise when intensity conditions are insufficiently separated or when measurement variability limits detection of small

incremental effects. Here, the intensity manipulation achieved clear separation between conditions, as ROM gains differed significantly between stretching intensities. This makes inadequate intensity differentiation a less convincing explanation for the null between-intensity effect on PPT and is more consistent with ceiling-type modulation within the tested range, particularly given the generally good inter-day repeatability of PPT under standardised testing conditions [178]. Accordingly, further studies with a wider range of stretching intensities are warranted to determine whether the apparent absence of a dose-response reflects true saturation or limited sensitivity within the intensity range tested.

Study IV. Exploring the feasibility, acceptability and preliminary efficacy of a Home-Based stretching program for adults with fibromyalgia: a prospective Pre-Post feasibility study [146]

Twelve participants (n = 12, all female) were recruited over 43 days. Table 3 shows the demographic and clinical characteristics of the participants. One participant withdrew from the study due to illness unrelated to the study.

Characteristic	
N	12
Age, mean (SD) years	46.2 (8.8)
Height, mean (SD) meters	1.69 (5.4)
Body mass index, mean (SD)	28.8 (5.0)
Time since diagnosis, mean (SD) years.	4.2 (3.6)
Time since first symptom onset, mean (SD), years.	14.3 (7.5)

Table 3. Demographic and clinical characteristics. (Adapted from study IV, Appendix D)

Two online focus-group interviews were conducted. Eight of the 11 participants were able to participate. Based on the qualitative interviews, we identified four major themes: (1) Factors motivating participation, (2) The advantages of exercising at home, (3) Influence of weekly communication and (4) Potential areas for improvement.

(1) Factors motivating participation captured why participants chose to enrol, including a wish to contribute to improved treatment options and a desire to learn practical strategies for incorporating exercise into daily life. Participation was also facilitated by the perception that the programme was manageable despite fluctuating symptoms.

(2) The advantages of exercising at home reflected a view that the brief sessions could be integrated into everyday routines and adjusted around work and family demands. Participants emphasised that the flexibility in when to exercise was particularly valuable on days with higher symptom burden.

(3) Influence of weekly communication described how weekly app-based contact provided reassurance and a sense of support, even when participants did not actively initiate communication. When minor modifications were needed, the app was viewed as an easy way to obtain guidance, and the monitoring was generally perceived as helpful rather than intrusive and was described as helpful for maintaining exercise consistency.

4) Potential areas for improvement highlighted recruitment as a practical challenge and suggested that clearer, more transparent communication about the limited study demands could improve enrolment. Participants also emphasised the need for clearer options to tailor the exercises to daily capacity and symptom fluctuation so the programme remains manageable across varying levels of function and sensitivity.

Self-reported adherence was high (91% ± 6.9%). The quantitative analyses revealed clinically relevant improvements in the FIQ-R total score and physical and mental health scores (Table 4). In contrast, no clinically relevant changes were observed in PPTs or ROM after the six weeks.

		Baseline	**Post-stretch**	**% difference**
FIQ-R	Total score	56.5 ± 16.6	44.5 ± 14.5	21.2
	Physical Function	14.3 ± 6.8	11.8 ± 5.3	17.5
	Symptoms	29.6 ± 7.5	22.8 ± 6.8	22.8
	Overall	12,. ± 4.7	9.5 ± 4.8	25.0
	Pain	5.8 2.6	4.6 ± 2.8	20.3
	Stiffness	5.8 ± 2.6	4.4 ± 2.6	23.2
SF-36	MCS	32.2 ± 5.9	36.0 ± 5.0	11.8

	PCS	36.3 ± 6.3	41.7 ± 7.7	15.0
	PPT – Tibialis Anterior	125.9 ± 32.2	108.4 ± 14.0	-13
	PPT – Trapezius	129.7 ± 36.3	126.9 ± 42.8	-2
	ROM	157.9 ± 20.5	159.8 ± 23.2	1,2

Table 4. Absolute values (means (SD) and percentage differences) for secondary outcomes. (Adapted from study IV, Appendix D)

The findings demonstrated that the intervention was feasible and acceptable, with some barriers related to participant recruitment and the adaptability of the exercises to individual needs and physical conditions that should be addressed before progression to the RCT (Study V).

Patients with FM often report intolerance to physical activity and may experience exacerbation of symptoms when initiating exercise programmes [18,179]. Therefore, despite the low-impact nature of the stretching protocol, it was essential to examine participants' responses to the daily routine. The findings extend current knowledge by demonstrating that daily stretching was well tolerated, with no adverse events or harms reported. Qualitative data further indicated that participants could complete the exercises even during periods of severe symptoms without symptom exacerbation.

Adherence was supported via app-based logging and brief weekly messages. Participants described logging as helpful for maintaining consistency without feeling monitored, and they valued having easy access to guidance when needed, consistent with prior suggestions that app support may strengthen motivation and adherence [180].

A strength of the study was the patient involvement in shaping the design and recruitment. The combination of qualitative and quantitative methods provided clinically useful insights into feasibility and perceived relevance. However, the one-arm feasibility design, small sample, absence of a control group, and lack of researcher blinding preclude conclusions about clinical efficacy.

Overall, the findings support progression to Study V to evaluate the clinical efficacy of home-based stretching in FM.

Extended discussion

The following discussion points are, in part, informed by a structured critical appraisal of Study IV using the JBI Critical Appraisal Checklist for Qualitative Research [181], supplemented by the JBI checklist for quasi-experimental studies to evaluate the quantitative components [182].

Study IV advances the current evidence on exercise interventions in FM by addressing a gap in the literature. Despite persistent adherence challenges, the literature is dominated by efficacy-oriented trials. By evaluating feasibility and acceptability, the study clarifies which delivery features appear feasible in a home-based setting. The findings justify progression to an RCT, while keeping symptom and function outcomes explicitly preliminary.

Braun and Clarke's thematic analysis is commonly presented as a structured sequence of steps, especially across coding, theme development, and theme review (Phases 2–4) [183]. In Study IV, however, these steps were not treated as strictly linear. Instead, the analysis involved repeated returns to the transcripts, moving between specific participant quotations and the emerging themes to refine the interpretation and ensure coherence. This back-and-forth approach is consistent with a hermeneutic interpretive framework [184].

The primary outcome was feasibility/participant experienced acceptability, yet sustained investigator contact during the intervention may increase participants' vulnerability to social desirability effects, in which participants accentuate positive experiences and minimise difficulties [185]. Although the focus group interviews were facilitated by an experienced researcher with no prior relationship to the participants, initial coding was undertaken by the investigator, which may still have biased the interpretation through selective attention to confirmatory narratives. The subsequent consensus-based review with the independent facilitator and a third researcher mitigates, but does not eliminate, this risk. Accordingly, the qualitative findings support acceptability, while acknowledging a risk that potential critical accounts were underrepresented.

The feasibility conclusions were also constrained by sample size and sex distribution, as well as self-selection and potential inclusion bias inherent in recruitment via patient networks and social media. This recruitment approach is likely to preferentially recruit individuals who are more motivated to participate in research, have higher self-efficacy, and may be more compliant with treatment [186–188], thereby inflating acceptability narratives and adherence estimates and reducing generalisability. Consequently, feasibility and acceptability are best interpreted as most applicable to similar subgroups,

with more limited transferability to individuals with greater symptom burden or fewer resources.

Turning to the quantitative components, interpreting pre-post changes warrants particular caution in a feasibility context. Although the published article refrains from claiming efficacy, describing *"clinically relevant improvements"* and *"promising clinical outcomes"* may nonetheless be read as implying benefit. In the absence of a control group, interpreting changes in a one-arm pre-post feasibility design is constrained. In FM, where symptoms fluctuate [16], pre-post changes may plausibly reflect regression to the mean [189] or expectancy effects [63,190]. In addition, reporting a wide range of outcomes increases the likelihood that some favourable results will occur by chance, potentially overestimating the strength of the quantitative findings. However, the quantitative component was designed to provide exploratory estimates to justify progression to, and inform the design of, the subsequent RCT, not as evidence of clinical effectiveness.

While the study was intentionally qualitative in emphasis, the article could have stated more explicitly how the quantitative data were intended to inform progression to the RCT. One way to accomplish this could have been to specify a priori progression criteria to determine whether the feasibility findings supported progression to a definitive RCT, and whether any design modifications would be required [191]. The main purpose of the quantitative outcomes was to provide an early indication of the short-term effect (i.e., as a practical go/no-go signal for proceeding to the RCT) and to lay the foundation for the sample size calculation. As written, this decision-making role is not fully transparent, and the quantitative findings may be read as generally supporting acceptability by default. Making the intended function explicit would strengthen the feasibility rationale.

Study V. Efficacy of a novel home-based stretching program on fibromyalgia symptoms: a randomised controlled trial [147]

Between October 24, 2024 and May 22, 2025, 89 patients were assessed for eligibility. 58 (65.2%) met the inclusion criteria. They were randomised 1:1 to the intervention group or the control group.

Across six weeks, the home-based stretching programme produced a statistically significant and clinically relevant improvement in overall FM

impact. The FIQ-R total score decreased by 9.7 points (95% CI −15.0 to −4.4; $p < 0.001$) in the intervention group, corresponding to an 18.7% improvement, which exceeds the 14% MCID benchmark. The control group showed no meaningful change (+0.8 points; $p = 0.66$). (Figure 3)

Secondary outcomes showed a broadly consistent pattern. Mental health-related quality of life (SF-36 MCS) improved by 5.0 points (95% CI 2.5 to 7.6; $p < 0.001$), which falls within published MCID ranges for MCS. PCS showed no significant interaction, but there were main effects indicating improvement over time and higher scores at follow-up in the intervention group. Mechanistic outcomes (PPTs and ROM) also favoured the intervention.

Adherence was high (mean 83%), and discontinuation was low (7%). No serious adverse events occurred. Per-protocol analyses were consistent with the intention-to-treat findings, supporting robustness of the findings.

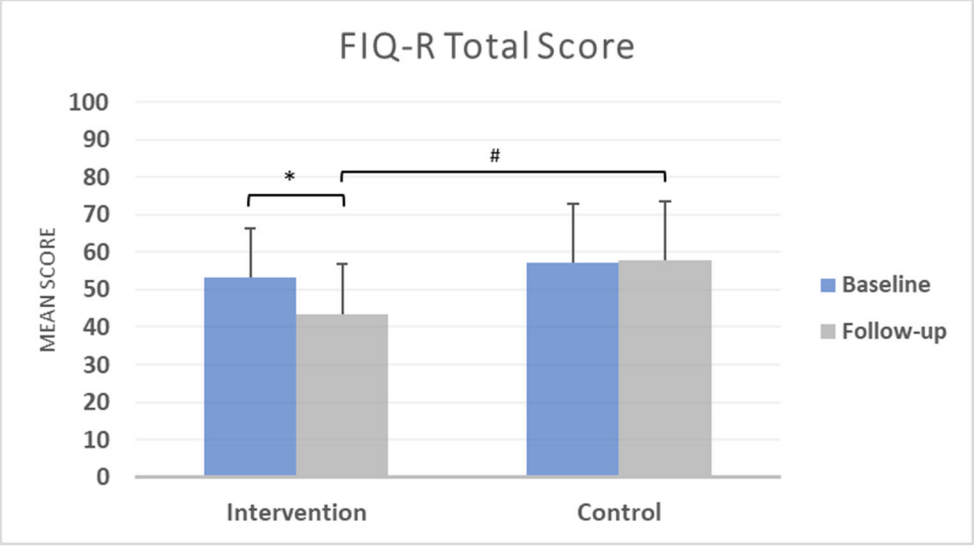

Figure 3. Mean (SD) FIQ-R total scores for the intervention and control groups at baseline and follow-up. Significant difference between (#) and within (*) groups ($p<0.05$). (Adapted from study Y, Appendix E)

The main findings showed that the home-based stretching intervention produced a statistically significant and clinically meaningful reduction in FM symptoms compared with usual care. Improvements exceeded the MCID

benchmark for the FIQ-R total score, supporting its potential as a feasible non-pharmacological treatment option.

The findings showed improvements in the FIQ-R and other core outcomes, broadly consistent with previous randomised trials and systematic reviews reporting modest benefits of stretching for FM symptom severity [96,144,167,192]. Compared with earlier reports [144,192], effects appeared larger, which may relate to high adherence and the low-impact, high-frequency format, although this was not formally tested.

A key strength of the study lies in its methodological rigour, as outlined in the published protocol (Appendix H) [148]. The involvement of patient partners and general practice collaborators enhanced clinical relevance and external validity. Treatment groups were comparable at baseline, exercise adherence was high, and discontinuation rates were low. Sensitivity analyses supported the robustness of the findings, lending confidence to the overall conclusions.

Key limitations include the inability to blind participants, which introduces potential expectancy effects on subjective outcomes. Unblinded outcome assessment may have biased the PPT results; however, the agreement between self-reported and objective outcomes suggests limited bias. The sample was predominantly female, restricting generalisability to men, particularly given possible sex-specific symptom differences [193]. The short intervention duration also precludes conclusions about long-term efficacy or sustainability.

Extended discussion

The following discussion points are, in part, informed by a structured critical appraisal of Study V using the Cochrane Collaborations RoB 2 tool for randomised controlled trials [173].

Study V adds to the current evidence by demonstrating clinically relevant effects of the low-intensity, high-frequency home-based stretching programme for FM. These findings strengthen the empirical basis for considering stretching as a standalone intervention option in this population

Consistent with RoB 2 [173], the usual-care waitlist design introduces a potential risk of bias for the primary outcome (FIQ-R). The allocation was unblinded; thus, the waitlist element created a potential expectancy asymmetry (i.e., participants knew whether they were receiving the

intervention immediately or only after follow-up). For symptom-based PROMs such as the FIQ-R and SF-36, this increases susceptibility to differential reporting driven by expectations, most plausibly biasing estimates away from the null (inflating improvement in the intervention group and attenuating change in controls). In addition, the waitlist design constrained longer-term follow-up, limiting inference regarding the durability of effects once structured trial support was withdrawn.

At the outset, the trial was not designed as a waitlist study. However, during protocol development, the user panel at the Centre for General Practice, Aalborg University, raised concerns about withholding access to a potentially beneficial intervention. Participants in Study IV subsequently echoed this view. This concern is particularly relevant in FM, where patients often report feeling dismissed or stigmatised in healthcare [26,82,194,195] and where current treatment options offer limited effectiveness [1,11,43]. In addition, Study II suggested that stretching may confer clinical benefits, further strengthening the rationale for ensuring access for participants allocated to usual care.

On this basis, the design was revised to include a waitlist control. The first protocol draft proposed conditional access for the control group, with the intervention offered following interim analyses if evidence of effectiveness emerged. However, this conditional-access approach was not approved by the regional ethics committee, which required the timing of access to be specified at recruitment. Consequently, a fixed waitlist design was adopted, in which control participants were offered to receive the intervention after completion of follow-up assessments. This supported transparency and informed consent, but it may also have amplified expectancy asymmetry, which should be considered when interpreting PROM-based outcomes.

In accordance with RoB 2 guidance for PROMs [173], participants were blinded to their own baseline FIQ-R, SF-36, and IPAQ responses, thus limiting the risk of anchoring to the baseline scores. Nevertheless, allocation unblinding remains a concern for bias, particularly where expectancy may influence symptom reporting.

The six-week intervention duration was selected pragmatically, as there is limited direct evidence to guide the optimal length of stretching programmes for improving core FM symptoms [10]. The decision was therefore anchored in the more established literature on ROM, which typically reports clinically meaningful gains after approximately 4 weeks of regular stretching [93]. This

timeframe was considered relevant because ROM improvements following stretching are thought to reflect increased stretch tolerance, which is closely linked to changes in pain sensitivity [89,98,143,196]. On this basis, a four-week exposure might have been sufficient to demonstrate sustained adaptations in healthy adults. However, given that people with FM frequently report exercise intolerance and fluctuating symptom severity, the duration was extended to six weeks to allow a more gradual accumulation of exposure. Importantly, because the primary purpose of Study V was to test clinical efficacy, the six-week duration also served as a pragmatic benchmark for a clinically relevant effect to have emerged if the intervention was efficacious. The six-week duration was also broadly consistent with the duration used in several prior stretching trials in FM, which reported improvements in relevant outcomes, even though those interventions differed in content and did not employ the same low-intensity, high-frequency prescription [160,162–164].

Self-monitoring and app-based logging were pre-specified components of the intervention, intended to support adherence rather than serve as ancillary trial procedures. Accordingly, these elements should be interpreted as part of the intended intervention and do not constitute an unintended co-intervention. A separate, more relevant concern is that the mode of weekly contact differed between groups (app contact versus email), potentially leading to an imbalance in attention and accountability. In the context of PROM-based outcomes, this could amplify between-group differences, although the likely magnitude of this bias is limited.

Missing data were handled using baseline-carried-forward imputation, which is generally conservative and would be expected to bias estimated effects towards the null [197]. This approach assumes that any participant with a missing post-intervention outcome would have the same value at follow-up as at baseline [198]. However, dropouts may have been related to perceived benefit or dissatisfaction with allocation, so this assumption may not hold equally across groups. Although this may affect the magnitude and precision of estimates, given the limited extent of imputation, any resulting bias is likely to be small. Per-protocol analyses produced findings consistent with the primary analysis, indicating that the conclusions were robust to assumptions about missing data.

Although the open-label design means that the magnitude of effect estimates remains susceptible to expectancy and reporting effects, credibility in the overall conclusion is strengthened by the broadly consistent effects across the primary endpoint (FIQ-R) and secondary outcomes (SF-36 MCS,

stiffness, PPTs, and ROM), reducing the likelihood that the conclusion depends on a single measure.

Finally, any statement about the clinical meaningfulness of the FIQ-R change requires qualification, because a universally accepted MCID for the FIQ-R is currently lacking. One study has proposed an MCID of 27 points for the FIQ-R total score [199], but this fixed threshold has important limitations. Because it is based on absolute change and does not account for baseline severity, it may be less attainable for individuals with low or moderate baseline scores, even when they experience meaningful improvement. Moreover, a 27-point reduction represents a very large proportional change in overall impact compared with MCID thresholds used for many other clinical measures. Consequently, applying this cut-off may notably underestimate clinically relevant improvement [200]. Accordingly, the observed between-group improvement in FIQ-R should be interpreted as supportive of clinical efficacy, while recognising that the proportion meeting any given "clinically meaningful change" threshold is sensitive to how MCID is defined.

Synthesis of contributions across Studies I–V

Aligned with the thesis aim, Studies I–V formed a staged programme from mechanistic work in healthy adults to feasibility and clinical evaluation in FM. The contributions of Studies I–V are summarised below in terms of how each study advanced the overall thesis aim.

Study I showed that regular stretching elicited significant reductions in regional and widespread pain sensitivity. This provided the mechanistic basis for examining stretching intensity as a valuable prescription parameter (Study III) and for progressing to clinical evaluation of a home-based stretching protocol in FM (Studies IV–V).

Study II showed that, although effects generally favoured stretching, certainty in the evidence was very low, and the interventions were highly heterogeneous, with recurring methodological limitations. This justified

standardising the protocol and strengthening the clinical evaluation in Studies IV–V to address key weaknesses in the existing trial literature.

Study III showed that local and widespread pain sensitivity decreased following acute stretching, regardless of stretching intensity, despite markedly larger ROM gains at higher intensity. This supported carrying forward a non-painful intensity target into the FM protocols in Studies IV–V, where tolerability and adherence were central.

Study IV showed that the intervention was feasible and acceptable in FM and informed refinements to intervention materials and study procedures for Study V. While effectiveness was not the primary focus, the quantitative results provided preliminary support for advancing the intervention to the RCT (Study V).

Study V operationalised the thesis aim by evaluating the clinical efficacy of the six-week, low-intensity, high-frequency home-based stretching protocol compared with usual care, building on the mechanistic, prescriptive, and feasibility findings from Studies I–IV.

Chapter 4. Conclusion

This PhD thesis evaluated stretching as a candidate intervention for FM through a range of studies progressing from mechanistic work in healthy adults to feasibility testing and clinical efficacy evaluation in FM, thereby strengthening the understanding of whether a standardised home-based stretching programme can produce clinically relevant improvements in FM-relevant outcomes.

Regular stretching was accompanied by systematic longitudinal changes in pressure pain sensitivity, including multisegmental hypoalgesia and partial retention after cessation (Study I). In addition, within the tested range, increasing perceived stretching intensity towards pain onset did not elicit greater acute hypoalgesia than an intensity defined by a clear stretch sensation (Study III).

The synthesis of the available evidence (Study II) indicated that stretching interventions generally favoured improvement in FM but were supported by very low-certainty evidence and substantial heterogeneity in intervention content and trial quality. Accordingly, progression to clinical evaluation required a clearly specified, standardised stretching protocol and a trial design intended to address recurrent limitations in the existing literature. Against this background, the mechanistic studies (Studies I and III) informed key features of the protocol development, including an intensity target defined by a stretching sensation rather than pain onset.

The thesis then demonstrated that the home-based, low-impact, high-frequency protocol could be delivered in a clinically relevant FM sample in a feasible and acceptable manner with indications of preliminary efficacy (Study IV). These findings therefore supported proceeding to clinical evaluation of the intervention. The low-impact, high-frequency home-based protocol was associated with improvements in FM-relevant symptom impact and related patient-reported outcomes compared with usual care (Study V), while recognising that inference remains contingent on the open-label context and the lack of longer-term between-group follow-up.

Chapter 5. Perspectives

Across the thesis, a key contribution to the current evidence was demonstrating that a low-impact, high-frequency home-based stretching intervention could be delivered with high adherence and low attrition in FM, supporting feasibility and acceptability in a format compatible with routine self-management. Importantly, the observed improvements of the intervention extended beyond pain sensitivity to FM-relevant domains, including symptom impact, aspects of health-related quality of life, mental and physical functioning, and stiffness. Given its low cost, simplicity and home-based delivery, the stretching intervention has plausible applicability across both primary and secondary care, particularly for individuals who are intolerant to exercise, sensitive to higher-intensity activity, or have struggled to sustain conventional exercise interventions. In this context, stretching may serve as an entry point to increase habitual activity levels and form the basis of a staged progression approach, with initial stretching supporting later uptake of cardiorespiratory and strengthening training when appropriate.

Future work warrants examining how the programme can be integrated into primary care and delivered across different contexts (e.g., general practice, municipal health centres, and private physiotherapy practices). In parallel, comparative evaluation of varying degrees of digital support, from app-only, minimal-contact delivery to the weekly support model used in this thesis, would help determine the level of support required to sustain adherence over time and whether these approaches are cost-effective compared with usual care.

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Appendices

Appendix A: Article 1

Appendix B: Article 2

Appendix C: Article 3

Appendix D: Article 4

Appendix E: Article 5

Appendix F: Article 6: Rebuttal

Appendix G: Article 7: Authors' reply

Appendix H: Article 8: Protocol article

Appendix A.

Study I

The effect of six-week regular stretching exercises on regional and distant pain sensitivity: an experimental longitudinal study on healthy adults. Støve, M. P., Thomsen, J. L., Magnusson, S. P. & Riis, A., 27 sep. 2024, I: BMC Sports Science, Medicine and Rehabilitation. https://doi.org/10.1186/s13102-024-00995-2.

Appendix B.

Study II

The effectiveness of stretching exercises in patients with fibromyalgia: A systematic review. Støve, M.P., Dissing, A.M.L., Magnusson, S. P., Thomsen, J. L. & Riis, A. Jun 2024, I: Clinical Rheumatology. https://DOI10.1007/s10067-024-07066-4.

Appendix C.

Study III

The effect of stretching intensity on pain sensitivity: A randomized crossover study on healthy adults. Støve, M. P., Hansen, L. Ø., Elmbæk, K. K., Magnusson, S. P., Thomsen, J. L., & Riis, A. (2025). European Journal of Pain, 29(3), Artikel e4750. https://doi.org/10.1002/ejp.4750.

Appendix D.

Study IV

Exploring the feasibility, acceptability and preliminary efficacy of a Home-Based stretching program for adults with fibromyalgia: a prospective Pre-Post feasibility study. Støve, M. P., Larsen, L. L., Magnusson, S. P., Thomsen, J. L. & Riis, A., 11 aug. 2025, I: Rheumatol Int 45, 191 (2025). https://doi.org/10.1007/s00296-025-05921-4.

Appendix E.

Study V

Efficacy of a novel home-based stretching program on fibromyalgia symptoms: a randomised controlled trial. Støve, M. P., Magnusson, S. P., Thomsen, J. L., & Riis, A. In review, Archives of Physical Medicine and Rehabilitation.

Appendix F.

A rebuttal to “The ineffectiveness of stretching exercises in patients with fibromyalgia: A systematic review discussion” — comments on “The effectiveness of stretching exercises in patients with fibromyalgia”. Støve, M.P., Dissing, A.M.L., Magnusson, S. P., Thomsen, J. L. & Riis. (2024). Clinical Rheumatology. https://doi.org/10.1007/s10067-024-07223-9.

Appendix G.

Authors' reply to the comment by Zhu et al. Støve, M. P., Hansen, L. Ø., Elmbæk, K. K., Magnusson, S. P., Thomsen, J. L., & Riis, A. (2025). European Journal of Pain, 29(1), Artikel e4770. https://doi.org/10.1002/ejp.4770.

Appendix H.

Efficacy of a home-based stretching programme on fibromyalgia symptoms: study protocol for a randomised controlled trial. Støve, M. P., Magnusson, S. P., Thomsen, J. L., & Riis, A. (2025). Trials, 26(1), Artikel 74. https://doi.org/10.1186/s13063-025-08776-z. (Appendix H)