Physical Activity in Hypermobile Ehlers-Danlos Syndrome and Generalized Hypermobility Spectrum Disorder

by

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ABSTRACT

Hypermobile Ehlers-Danlos Syndrome and Generalized Hypermobility Spectrum Disorder (hEDS/G-HSD) are two connective tissue disorders that are tightly intertwined as they both result in joint hypermobility-induced musculoskeletal manifestations and are placed on the same clinical spectrum. The combined prevalence of hEDS and G-HSD is estimated to be between five to eight out of 5,000, with a higher occurrence in women. These disorders solely rely on symptom prevention and management as there is no known cure. Physical activity is thought to be the most effective treatment for disorder management as it may reduce many commonly experienced symptoms by people with hEDS/G-HSD. This thesis aimed to assess the current evidence for PA as a management strategy and its uptake in people with hEDS or G-HSD by 1) determining the effectiveness of PA interventions on various symptoms and 2) identifying the habitual PAs as well as the barriers and facilitators to PA of Canadians with hEDS/G-HSD.

A scoping review identified 11 PA trials consisting of strengthening, balance and proprioceptive exercises. The results from both low- and high-load strengthening programs suggest that they can improve muscle strength and endurance, joint stability and reduce joint laxity, which in turn can reduce the risk of injury and disabling symptoms. Most studies demonstrated an improvement in pain score, balance, proprioception and functional capabilities as well as a reduction in disability for light-resistance PA interventions. High-resistance PA programs showed these same benefits in all outcomes, except for proprioception and balance. Other frequent symptoms such as fatigue and kinesiophobia also improved following both types of resistance-based PA interventions. The current evidence for PA as a treatment for hEDS/G-HSD suggests that it can reduce the burden of many symptoms and mitigate disability.

A survey was conducted in 186 Canadians with hEDS/G-HSD in which the median age of the sample was 42 and 88% identified as being a woman. Despite the benefits of PA, in a typical week, Canadians with hEDS/G-HSD underperformed PA, notably vigorous and muscle-strengthening activities. Barriers to PA were omnipresent, with the most common being symptoms, weather and a belief that PA makes symptoms worse; PA was most facilitated by support from family and

friends. Total score for the Inflammatory Arthritis Facilitators and Barriers-derived questionnaire was strongly associated with duration of muscle-strengthening and moderate PAs in multivariate regression analyses, as well as the probability of participating in vigorous PA and meeting the Canadian Movement Guidelines in logistic regressions. Other important predictors were inability to work and the use of support aids, both reducing the likelihood and duration of PA participation.

These results suggest that while PA can be beneficial for hEDS/G-HSD symptom management, it is poorly undertaken by people with hEDS/G-HSD. Barriers and facilitators have a strong role in predicting whether people with hEDS/G-HSD participate in PA; unfortunately, barriers to PA are widespread in this population. Recommending PAs in function of people's barriers and facilitators can be crucial for the uptake and maintenance of PA, and nurturing health and wellbeing in individuals with hEDS/G-HSD.

PREFACE

This thesis is an original work by Annecy Houston. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name “Physical activity behaviors barriers and facilitators in hypermobile Ehlers-Danlos syndrome and generalized hypermobility spectrum disorder”, No. Pro00124933.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 CHAPTER 1: Introduction

1.1 Background: Joint Hypermobility

Joint hypermobility is a condition in which a joint has a range of motion that exceeds the norm.[1] It can be inherited or acquired through environmental means.[2–5] When multiple joints are considered hypermobile, it is termed generalized joint hypermobility (GJH). GJH is a condition in itself as well as a symptom of broader disorders such as some connective tissue disorders. Abnormalities in the connective tissue components (i.e., ligaments or tendons) are seen in connective tissue disorders and can be expressed mechanically as in the case of two hypermobile disorders: hypermobile Ehlers-Danlos Syndrome (hEDS) and generalized hypermobility spectrum disorder (G-HSD). In both hEDS and G-HSD, GJH is a core symptom that frequently induces other symptoms.

G-HSD and hEDS are connective tissue disorders with unidentified genetic mutation and with an unknown pathogenesis[4,6] Currently, the clinical diagnosis of hEDS and G-HSD differ slightly. hEDS must have the simultaneous presence of 3 criteria: (1) evidence of GJH using the Beighton score measuring hypermobility of the fingers, thumbs, elbows, knees and spine; (2) two of the following: the presence of at least five other systemic connective tissue manifestations, family history, and pain or instability; and (3) exclusion of an alternate diagnosis.[5] Systemic connective tissue manifestations include: soft or velvety skin; mild skin hyperextensibility; unexplained striae; bilateral piezogenic papules of the heels; recurrent or multiple abdominal hernias; atrophic scarring; dental crowding and high or narrow palate; arm span-to-height ratio of at least 1.05; mitral valve prolapse; aortic root dilation with Z-score over two; arachnodactyly as defined as long and slender fingers; pelvic floor, and; rectal and/or uterine prolapse.[5] If five or more of the aforementioned manifestations are simultaneously present in an individual, they are considered to have evidence of a connective tissue disorder. [5] A G-HSD diagnosis is made when an individual has GJH with one or more secondary musculoskeletal manifestations.[7]

The combined prevalence of hEDS and G-HSD is estimated to be as high as eight out of 5,000, however an accurate prevalence of hEDS/G-HSD is still unknown.[8] Current research has shown a higher prevalence of hEDS in women than in men.[9–11]

G-HSD and hEDS are tightly intertwined uncurable conditions as they both result in hypermobility-induced manifestations and share similar phenotypes.[12] They are frequently paired in research as they are thought to be entities on the same clinical spectrum.[3,13] For this reason, the research project herein considers both disorders together.

1.2 hEDS and G-HSD Manifestations

Joint stability depends on ligaments, muscles, tendons, joint capsules and body congruency, therefore dysfunction in any of these components can result of hypermobility.[2] A hypermobile joint can impact the biomechanics of the body by inducing compensatory changes, which may increase the risk of musculoskeletal manifestations.[2] Not only do joint injuries occur more frequently in individuals with hEDS/G-HSD,[14,15] but this population is also slower to recover from injuries, potentially as a result of their low-quality connective tissue.[16,17]

Hypermobile joints can be easily stressed, which makes people with hEDS/G-HSD susceptible to repetitive use and soft tissue injury, muscle strain and spasms, and osteoarthritis.[2,18] Additionally, people with hEDS/G-HSD are prone to joint subluxations and dislocations, tendonitis, tendon ruptures, muscle and ligament tears as well as muscle tension and spasm.[4,19,20] Nociceptive and neuropathic pain in both the joints and limbs have been reported in hEDS/G-HSD. Pain is frequently rated as severe.[9] Coordination, balance and proprioception are also often diminished.[12,14,18,21] These features are often accompanied by gait abnormalities[22] (i.e., slower gait velocity and narrower base of support), excess plantar flexion during stance and decreased dorsiflexion during swing.[18] The risk for these occurrences are heightened due to this population's propensity for low muscle strength, endurance, functional performance and lean mass, as well as their greater fat mass, compared to other populations.[12,21,23,24]

Symptoms reported by individuals with hEDS or G-HSD may also go beyond the musculoskeletal system.[3,15,25] People with hEDS/G-HSD also frequently report fatigue, gastrointestinal dysfunction, migraines and headaches, autonomic system dysfunction and mast cell dysfunction, with a wide variability of prevalence and severity.[3,15] Manifestations experienced by people with hEDS and G-HSD also extend to rheumatological[9,15], psychiatric[18,26], genitourinary[25], respiratory[9,27], and gynecological dysfunction and complications during pregnancy.[12]

Given the high propensity of typical hEDS/G-HSD musculoskeletal and non-musculoskeletal symptoms co-appearing, individuals with these disorders may face activity limitations.[18,25,28] People with hEDS/G-HSD may report difficulty maintaining their usual daily functions, social life, attending school and tending to their occupations, triggering guilt and shame for losing autonomy.[28]

1.3 Physical Activity for Symptom Management

Individuals with hEDS and G-HSD must adopt multiple management strategies for their specific symptoms and circumstances as a single strategy is often insufficient on its own.[18,29,30] For this reason, a multidisciplinary approach combining patient education, pharmacological treatment, nutritional supplements, psychological therapy and physical therapy is generally recommended.[2,4,19,20]

Physical activity (PA) is considered a key component of symptom prevention and management. PA is defined as all energy-requiring movement of the skeletal muscles, and includes light (i.e., standing, walking, wheeling) to vigorous (i.e., running, cycling, swimming) exercise.[31] The optimal amount of PA for 18–64-year-olds recommended by Canada's Movement Guidelines is a minimum of 150 minutes of moderate to vigorous exercise per week, and muscle-strengthening activities twice a week.[32] Healthcare providers such as physiotherapists, rheumatologists, physiatrists and geneticists especially recommend that individuals with hypermobility adopt a habit of being physically active to maintain optimal health and wellbeing.[1,33] Physical therapies used to manage

hEDS/G-HSD symptoms include exercise, including cardiovascular training, proprioceptive work and strengthening.[15,16,18,33,34]

PA can decrease the risk of many chronic and acute health conditions as well as all-cause mortality in the general population.[35] Exercises, often prescribed by a physiotherapist, can be used to improve strength in the muscles surrounding joints, core stability, motor control, body awareness, posture and endurance, and minimize the severity of many symptoms experienced by people with hEDS or G-HSD.[2,20,33,36,37] Physiotherapy consisting of strengthening and proprioceptive work with slow intensity and frequency increments is considered the most successful therapy for pain, but can be effective for fatigue, autonomic dysfunction, balance and coordination, pain sensitization as well as to decrease functional challenges and prevent physical deconditioning and injury.[38] PA's benefits require consistent effort and time to achieve, especially in people with hEDS/G-HSD given the higher likelihood of symptom aggravation or injury.[25]

There is currently no widely accepted evidence-based PA program for individuals with hEDS/G-HSD, however some hEDS-specific muscle-strengthening programs have been piloted in pre-post studies and randomized trials. Rehabilitation trials demonstrate that participants enrolled in a PA program can reduce pain and fatigue, and increase muscle strength and endurance, functional abilities, proprioception, balance, and kinesiophobia – a fear of injury due to movement. [21,38–48]

Despite the apparent benefits of PA, Simmonds et al. (2019) reported that only 47% of individuals with hEDS/G-HSD participated in 60 minutes or less of PA weekly. This raises the query: what predicts the uptake and regular implementation of PA in people with hEDS or G-HSD?

1.4 Barriers and Facilitators to PA

To our knowledge, there is only one study describing the PA habits and barriers in individuals with hEDS and G-HSD, which was based in the United Kingdom.[11] The majority of the 946 participants were white females between 18 and 40 years of age with a university education. [11] Approximately 26% of the study participants either didn't exercise or exercised for less than 30 minutes, 21%

exercised for between 30-60 minutes, 27% identified exercising for 1.5-2.5 hours and 26% reported exercising for over 2.5 hours.[11] The participants' volume of exercise was associated with advice from physiotherapists, employment, physical balance, and beliefs that PA is helpful for long-term management, pain control, wellbeing and mental health.[11] Individuals reported pain, fatigue and fear of injury as barriers to PA.[11] However, rheumatology studies that evaluated barriers and facilitators for individuals with fibromyalgia, rheumatoid arthritis, spondyloarthritis or psoriatic arthritis described a wider range influences on PA participation.[49,50]

This thesis fills a knowledge gap by assessing the duration of PA in different intensity zones and types, and thoroughly investigating the barriers and facilitators to PA, and their impact on PA behaviours in Canadians with hEDS and G-HSD. This information can be used when prescribing and encouraging the maintenance of a rehabilitation program for symptom management in this population.

1.5 The Research Project

The project herein aimed to identify the current PA habits of Canadians with hEDS and G-HSD. Specifically, the average length of time spent doing moderate, vigorous and strength-training activities, stretching, walking and sitting over a typical 7-day period was investigated. Additionally, this study also quantified the associations of various barriers and facilitators on PA, which no other study has done in individuals with hEDS/G-HSD.

The methods are described in detail in Chapter 3. Briefly, this information was collected through an online survey platform (REDCap) where participants were recruited from one of three ways: a newsletter from a partner hEDS/G-HSD organization, support groups on Facebook or the office of a single physician specialized in hEDS/G-HSD. The survey was based on questionnaires that were validated in previous research,[50–55] and adapted to the needs of people with hEDS and G-HSD. One hundred and eighty-eight people responded to the survey between February and March, 2023.

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2.0 CHAPTER 2: Review for Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorder

2.1 Introduction: Defining the Hypermobility Syndromes

A hypermobile joint is defined as the movement of a synovial joint beyond a normal range and is influenced by factors such as age, ethnicity, sex, physical activity, injury, disease or infection, and genetic risk factors.[1–4] Generalized joint hypermobility (GJH) is termed when hypermobility is present in joints all over the body, as opposed to locally or peripherally. GJH is estimated to affect 12.5% of the general population, with a higher prevalence in females.[1–4]

GJH can present asymptomatically or symptomatically[5], and manifest on its own or be inherited as part of a connective tissue disorder.[1] When GJH is symptomatic, it is termed G-HSD where severity varies on a spectrum.[6] It is thought that towards the end of this spectrum, hEDS is found (Figure 2.1).[6] G-HSD and hEDS are tightly intertwined conditions as they lie on the same clinical spectrum and share similar hypermobility-induced symptoms. [2,6,7]

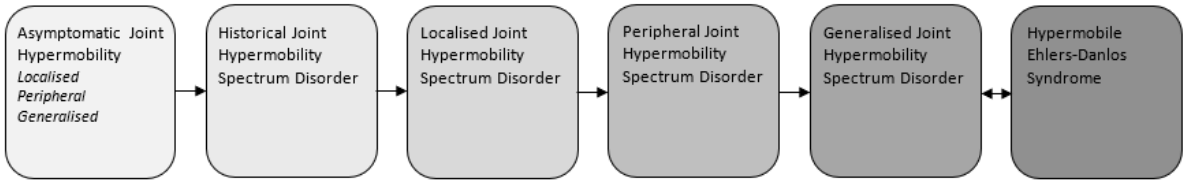

Figure 2.1 Hypermobility Spectrum. Range of hypermobility spectrum disorders where generalised hypermobility spectrum disorder is tightly intertwined with hypermobile Ehlers-Danlos syndrome.[12]

The combined prevalence of hEDS and G-HSD is estimated to be between one to two out of 1,000, however an accurate prevalence is unknown.[8] Diagnosis of these conditions relies on clinical presentation as the genetic markers for hEDS and G-HSD remain unknown.[4] In 2017, the International Consortium on the Ehlers-Danlos Syndromes & Related Disorders[4] updated diagnostic criteria for hEDS, succeeding the previously used Villefranche[9] and Brighton criteria.[10] The criteria include: (1) presence of GJH as evaluated by the Beighton score;[11] (2) at least two of the following: evidence of a systemic connective tissue disorder, a positive family history, and pain

and/or instability; and (3) exclusion of an alternate diagnosis.[4] Systemic connective tissue manifestations include: soft or velvety skin; mild skin hyperextensibility; unexplained striae; bilateral piezogenic papules of the heels; recurrent or multiple abdominal hernias; atrophic scarring; dental crowding and high or narrow palate; arm span-to-height ratio of at least 1.05; mitral valve prolapse; aortic root dilation with Z-score over two; arachnodactyly as defined as long and slender fingers; pelvic floor, and; rectal and/or uterine prolapse.[4] If five or more of the aforementioned manifestations are simultaneously present in an individual, they are considered to have evidence of a connective tissue disorder. [4] A G-HSD diagnosis is made when an individual has GJH with one or more secondary musculoskeletal manifestations.[12]

hEDS and G-HSD (hEDS/G-HSD henceforth) are multisystemic disorders with a strong impact on the musculoskeletal system. Due to GJH, joints tend to be unstable and easily stressed, which makes them susceptible to pain, sprains, subluxations and dislocations. These conditions are also associated with tendon, ligament and muscle tears, muscle tension and spasms, and degenerative joint and bone disorders (i.e., osteoporosis).[1,13] The risk for these occurrences are further heightened due to people with hEDS/G-HSD's propensity for low muscle strength, endurance and lean mass, as well as poor coordination, balance, proprioception and functional performance.[6,13–17]

hEDS/G-HSD symptoms extend beyond musculoskeletal. Fatigue, migraines and headaches, gastrointestinal dysfunction, rheumatological diseases, autonomic disorders such as postural orthostatic tachycardia syndrome (POTS) and psychiatric disorders, also occur with a wide variability of prevalence and severity.[2,18] Physical and psychological comorbidities are common in hEDS and often challenge participation in maintaining usual daily functions, social life, attending school and working.[19]

Symptom management is at the core of hEDS/G-HSD wellness.[1] Physical activity (PA) is defined as all energy-requiring movement of the skeletal muscles.[20] It can range from everyday activities such as walking to a bus stop to light spiritual practices such as tai chi to more intense activities such as

long-distance cycling or powerlifting.[20] It is considered an important management strategy for hEDS and G-HSD and is widely recommended to prevent or treat various hEDS/G-HSD-related symptoms as well as to maintain general health.[1] Herein, we detail the rationale for PA as a symptom management tool, and the current evidence of PA for the treatment of joint laxity; instability or range of motion; muscle strength and endurance; pain; functional abilities and disability; proprioception and balance; fatigue, and; kinesiophobia in people with hEDS/G-HSD.

2.2 Methods

One author (AH) searched Ovid Medline, Ovid Embase, SCOPUS, CINAHL and CENTRAL for scientific articles published in either English or French from the date of inception to December 5th, 2023. Studies using a pre-post or trial design were considered for inclusions. Furthermore, completed, full-text and published studies assessing any physical activity or exercise intervention of any duration in adults with hEDS and/or G-HSD with any concurrent intervention and for any joint were included. A comparison to pre-treatment in the same individual, or to any or no intervention in a control group qualified for inclusion. Eligible studies reported on at least one of the following outcomes: joint laxity, instability or range of motion, muscle strength and endurance, pain, functional abilities and disability, proprioception and balance, fatigue and kinesiophobia. All outcomes were extracted in an unvalidated Excel sheet and reported in this scoping review, grouped by low- or high-resistance program. Grey literature, abstract-only publications, reviews and animal studies were excluded.

Keywords and indexed terms relating to hEDS or G-HSD and physical activity were used and linked using Boolean operators without limitations (Supplementary Materials 1). The search strategy was based on a search hedge for exercise, physical activity, play and sport,[21] and developed according to recommendations from a health science librarian. The same author triaged the initial list of articles using Covidence. Figure 2.2 displays the PRISMA flow diagram of articles triaged.

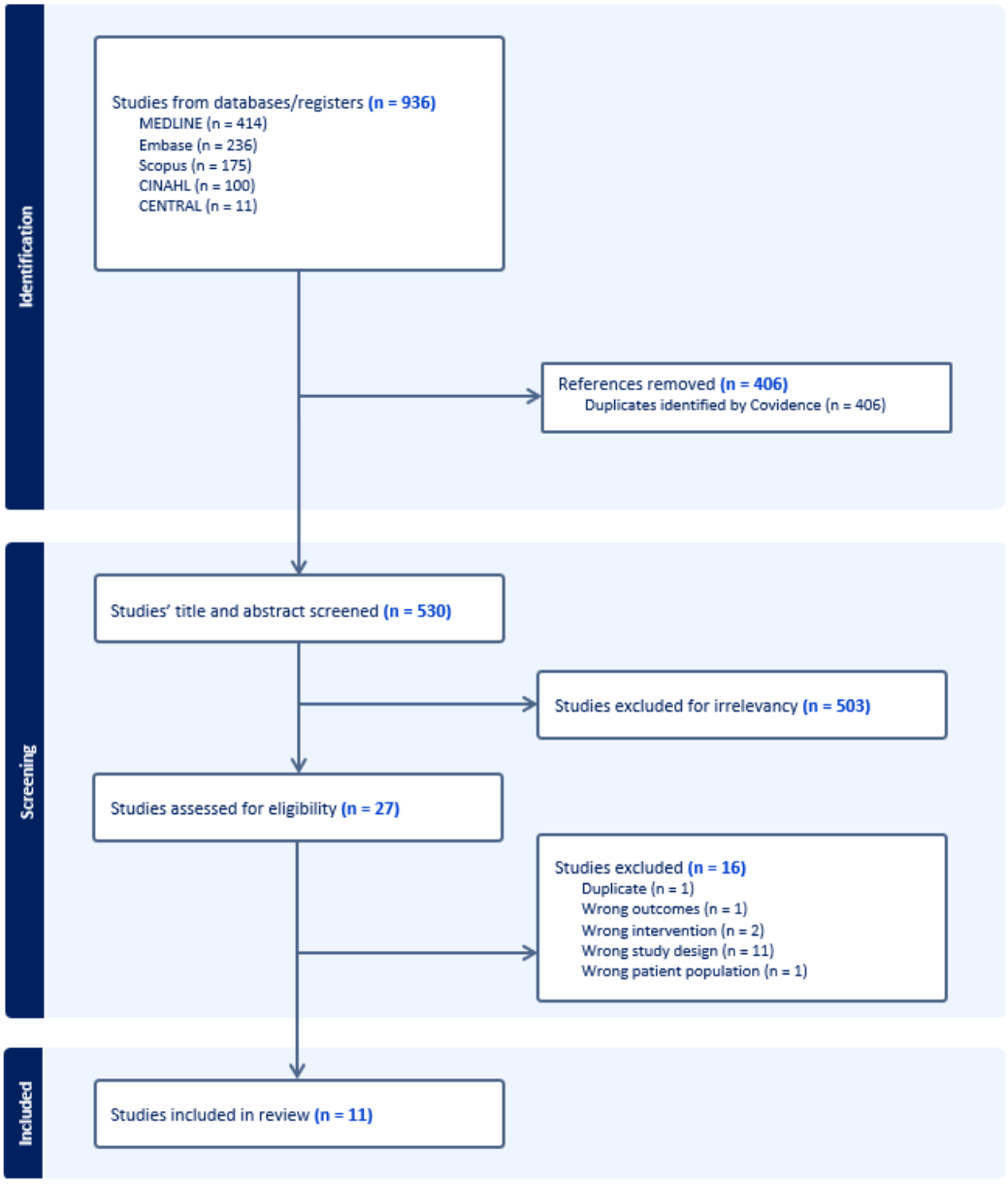

Figure 2.2 PRISMA Diagram. Diagram demonstrating the triage process of research articles found as a result of the search strategy. Nine hundred and thirty-six articles were initially found in the identification stage, but only 11 were included in this scoping review.

2.3 Physical Activity and Symptomatic Hypermobility

Eleven high- (n = 3)[15,17,22] and/or low-resistance (n = 8)[15,23–30] rehabilitation programs have been trialed in people with hEDS/G-HSD (Table 2.1). Seven of the included studies were randomized two-group trials,[15,17,24–27,29] and four evaluated the knees[17,26,29,30] and three assessed the shoulder joints.[15,22,24]

High repetition of low-resistance and low-impact exercises are currently the standard recommendation for the management of hEDS/G-HSD symptoms among clinicians,[13,15,31,32] and are the most studied in the literature.[24–30] Low-resistance PA consisted of activities where light loads were used; these types of programs included joint and core stability, balance and proprioception exercises.[23,24,26–30] Progressions were generally made every few weeks by increasing duration or frequency, adding further resistance and/or additional stability challenges.[15,23–27,29,30]

More recently, high-resistance programs have been tested among people with hEDS/G-HSD.[15,17,22] These primarily involved high loads for muscle-building, and stability exercises at a high resistance for up to 12 repetitions, with weight progressions.[15,17,22] Overall, the 11 included studies suggest that symptoms experiencing by people with hEDS/G-HSD can benefit from both program types.[15,17,22–30]

Table 2.1 Summary of Study Characteristics

Study	Study Design	Setting	Sample	Target area(s)	Intervention	Duration
Ferrell et al. (2004)	Pre-post study	Home-based	18 adults with G-HSD (Brighton criteria)	Knees	Physiotherapy regimen comprising of closed kinetic chain exercises such as squats, pliés, bridges, side lunges and front lunges as well as a static hamstring exercise with weekly reps and set progressions.	4 days per week for 8 weeks
Sahin et al. (2008)	Randomized controlled trial	Under control of a doctor in clinic	EX: 15 adults with G-HSD (Brighton criteria) CO: 25 adults with G-HSD (Brighton criteria)	Knees	EX: kinesthesia and balance exercises with weekly progressions: walking backward, heel walking, walking on fingertips, walking with eyes closed, standing on 1 extremity, bending forward–backward-sides on 1 extremity, slowly sitting on a high chair and standing up. CO: no exercise	3 days per week for 8 weeks
Bathen et al. (2013)	Pre-post study	Hospitalized for rehabilitation and home-based training period	12 women with hEDS/G-HSD (Villefranche and Brighton criteria)	Full body	2 ½ weeks: in-patient in a rehabilitation unit with testing, physical training, group discussions and lectures. 12 weeks: individual home exercises (squats, elastic band rowing, sit-ups, glute bridges, wall push-ups and back, pelvic floor and core stability exercises) with weekly guidance by a physiotherapist.	2 ½ weeks in-patient and 12 weeks out-patient with 5 sessions
Toprak Celenay et al. (2017)	Randomized controlled trial	Yildirim Beyazit University's Physiotherapy and Rehabilitation Department's exercise room	EX: 20 women with G-HSD (Brighton criteria) CO: 18 women with G-HSD (Brighton criteria)	Trunk and lower limb muscles	EX: sessions consisted of 10 min warm-up exercises, 25 min stabilization exercises, 5-10 min cool-down, and stretching exercises. Week 1-2: static lumbar bracing in supine and prone lying, 4-point kneeling, sitting, standing positions Week 3-5: bracing during dynamic exercises with resistance bands Week 5-8: bracing with functional exercises resistance bands and balance exercises CO: no exercise or sport during study period	40-45 minutes sessions, 3 days a week for 8 weeks
Daman et al. (2019)	Single-blind randomized controlled trial	Shiraz School of Rehabilitation Sciences under the supervision of a physiotherapist	EX: 12 adults with G-HSD (Brighton criteria) CO: 12 adults with G-HSD (Brighton criteria)	Knees	EX: squatting exercises, bridging, pliés, backward walking, heel walking, walking on toes, walking with eyes closed, standing on 1 leg, and bending back and forth on 1 leg with eyes closed and with eyes open, with weekly progressions. CO: no intervention	3 days per week for 4 weeks
Reychler et al. (2019)	Single-blind randomized controlled trial	Home-based	EX: 9 adults with hEDS (Villefranche and Brighton criteria) CO: 10 adults with hEDS (Villefranche and Brighton criteria)	Inspiratory muscles	EX: while wearing a nose clip and being comfortably seated, patients were asked to inspire through the threshold inspiratory muscle training for 6 sets of 10 reps with progressively increasing resistance ranging from 60% to 85% of the initial maximal sniff nasal inspiratory pressure. CO: no intervention	5 weekly sessions for 6 weeks

Liaghat et al. (2020)	Pre-post study	Physiotherapy clinic supervised by a physiotherapist twice weekly and self-managed once weekly	12 adults with G-HSD	Shoulders	Heavy shoulder strengthening exercise: side lying external rotation in neutral, prone horizontal abduction, prone ER in 90° of shoulder abduction, supine scapular protraction and seated shoulder elevation in the scapular plane. Week 1–3: familiarization period with 3 sets of 50–90% of 10 RM Week 4–9: 3 sets of 10 RM Weeks 10–15: 4 sets of 8 RM Week 16: tapering period	16 weeks, 3 times per week
Luder et al. (2021)	Single-blind randomized controlled trial	Berne University Hospital medical training center with a physiotherapist available during training	EX: 27 adults with GJH CO: 24 adults with GJH	Knees	EX: 50-minute resistance training session focused on leg and trunk muscles. Resistance was 80% of the 1RM and 3 x 12 reps per side. Assessment of exercise quality and resistance was revisited at week 3 and 6. CO: no intervention	12 weeks, 2 days per week
Spanhove et al. (2022)	Single-blind 2-group randomized trial	Home-based	EX: 11 women with hEDS or G-HSD (2017 criteria) CO: 10 women with hEDS or G-HSD (2017 criteria)	Shoulders	2 programs consisting of 4 exercises within 3 phases of increased difficulty: Phase A: patients exercised daily Phase B: 5 times per week Phase C: minimum of 3 times per week EX: tailored to patients and based on the latest hEDS/G-HSD research: shrugs, external rotation, bench slides and wall slides, all with progressions in each phase. CO: a standard rehabilitation program of balance and proprioception, isometric strength, rotator cuff muscles and open chain elevation exercises.	24 weeks
Liaghat et al. (2022)	2-group randomized trial	Physiotherapy clinics near participants' homes	EX (heavy program): 34 adults with HSD CO (light program): 33 adults with HSD	Shoulders	EX: the heavy strength training program consisted of 5 exercises at 50% of 10 RM, increased by 20% after week 1 and week 2. Week 6 onwards, 3 sets of 10 RM were completed. CO: the low-resistance program consisted of 9 shoulder exercises including isometric posture correction until week 5, isometric shoulder exercises until week 11, after which a yellow Theraband was introduced.	16 weeks
Hakimi et al. (2023)	Nonrandomized controlled trial	Outpatient multidisciplinary service	EX: 19 adults with hEDS (2017 criteria) CO: EX group, but 9 weeks prior to intervention start	Full body	EX: 4 one-hour workshops of the following: occupational therapy, physiotherapy, sophrology, physical activities focused on muscular endurance, coordination, balance and proprioception, or therapeutic patient education workshops. CO: no treatment changes.	9 weeks: 2 days per week during 4 weeks, followed by 1 week of rest and 4 weeks including 3 days per week

Experimental group (EX); Control group (CO); Repetitions (reps); Repetition maximum (RM).

2.4 Exercise and hEDS/G-HSD: The Evidence for Symptom Prevention and Treatment

2.4.1 Instability, Joint Laxity and Range of Motion

When connective tissue is mechanically weak, it tends to be lax, range of motion tends to be larger, and joints tend to become more unstable. This can result in a joint being easily stressed and injured (i.e., subluxations and dislocations), causing pain and loss of function.[1,13,] Reducing connective tissue laxity and range of motion can be challenging,[33] but instability can be reduced by strengthening the muscles surrounding a joint. [1,32,34–36]

Two studies reported on instability, joint laxity and range of motion of the shoulder (Table 2.2).[15,22] The results from the high- and low-resistance interventions suggest an increase in stability, with a larger impact in the former groups.[15,22] This extends to joint laxity as well;[15,22] laxity was higher among those trialing the low-resistance program when compared to high-resistance programs.[15] The pre-post study indicated reduced laxity following the heavy exercise intervention.[22]

Results were inconclusive regarding range of motion. One study reported a decrease in most shoulder range of motion measurements, which is desirable in hEDS/G-HSD.[22] In Liaghat et al. (2022), no pre-program measurements were taken for range of motion;[15] however, in this randomized study, the light-resistance program participants had a larger average range of motion than those that participated in the high-resistance program following the study when assessing active and passive internal and external rotations.[15] Due the predisposition of a high range of motion, it would be favourable for a decrease in range of motion, even though muscle-strengthening PAs generally augment range of motion. [33] According to the results from these two studies, range of motion may be diminished using PA.

2.4.2 Muscle Strength and Endurance

Individuals with hEDS/G-HSD are at higher risk of injury[17,18] and tend to be slower to recover once injury occurs.[37,38] The risk for injury is heightened due to this population's propensity for low muscle strength and endurance. [6,14–16] In one study of individuals with hEDS, joint problems and muscle problems were present in 84.8% and 64.6% of the sample, respectively.[39] Furthermore,

muscle strength and endurance can be important indicators for the likelihood of experiencing joint instability and pain.[40]

Assessment methods for muscle strength and endurance vary widely across trials in hEDS/H-HSD; however results seem favourable regardless of outcome measure and program type (Table 2.2).[15,22,25,27,28,30] Low resistance programs showed that muscle force improved following a low-resistance programs, and beyond that of controls.[15,25,30] For a similar intervention, stair-climbing and -descending, and tandem walking backwards for a certain distance was performed faster than before the exercise program.[28] The six-minute walking test, where the walking distance is recorded for six minutes, also improved compared to baseline[23,25] and control periods.[23] Not only did dynamic endurance increase, but static holds were also held longer.[27]

High resistance programs also demonstrated that they could improve the maximum voluntary contraction of knee and shoulder muscles.[15,22] Endurance has not been tested yet in a high-resistance rehabilitation intervention.

Table 2.2 Pain, Muscle Strength and Endurance, and Hypermobility Outcomes of Trials

Study	Timepoint	Outcomes: MD (95% CI)*		
		Pain	Muscle Strength/Endurance	Joint Instability, Laxity and Range of Motion
Ferrell et al. (2004)	Week 8	VAS10:-1.9 (n/a)	QUAD peak torque: 3 N/m (n/a) QUAD average torque: 13.6 N/m (n/a) HAM peak torque: 13 N/m (n/a) HAM average torque: 5 N/m (n/a)	
Sahin et al. (2008)	Week 8	EX: VAS10 resting:-1.87 (n/a) CO: VAS10 resting:-0.04 (n/a) EX: VAS10 movement:-4.04 (n/a) CO: VAS10 movement:-0.08 (n/a)		
Bathen et al. (2013)	Week 14 ½	NRS: 0 (n/a)	Tandem walking backwards (MedD): -9.05 s (n/a) Stair climbing (MedD):-0.13 s (n/a) 30 s max reps calf raises (MedD): 4.50 (n/a) Stair-descending (MedD):-0.19 s (n/a)	
Toprak Celenay et al. (2017)	Week 8	EX: VAS10 MedD:-1.6 (-10.0; 0.0) CO: VAS10 MedD: 0.0 (-6.2; 8.9)	EX: MedD FLEX: 24.5 s (-44.0; 68.0) CO: MedD FLEX: 2.0 s (-27.0; 30.0) EX: MedD EXT: 28.5 s (-70.0; 111.0) CO: MedD EXT: 2.5 s (-55.0; 96.0) EX: MedD rLAT: 32.0 s (-35.0; 106.0) CO: MedD rLAT: 0 s (-27.0; 40.0) EX: MedD lLAT: 29.5 s (-28.0; 85.0) CO: MedD lLAT:-0.5 s (-27.0; 34.0)	
Daman et al. (2019)	Week 4	EX: VAS10: -2.73 (n/a) CO: VAS10: 0.5 (n/a)		
Reychler et al. (2019)	Week 7		EX: 6MWT: 64 m (5; 121) CO: 6MWT: 8 m (-5; 19) EX: sniff nasal inspiratory pressure: 13 (6; 20) CO: sniff nasal inspiratory pressure: -3 (-6; 1)	
Liaghat et al. (2020)	Week 16	NRS best: -0.9 (-1.7;-0.2) NRS worst: -2.5 (-3.8;-1.2) NRS average:-2.4 (-3.7;-1.2)	MVC scaption: 0.51 Nm/kg (0.23; 0.78) MVC internal rotation: 1.32 Nm/kg (0.70; 1.95) MVC external rotation: 0.89 Nm/kg (0.37; 1.40)	Internal active rotation ROM:-3.5 (-12.4, 5.3) External active rotation ROM: 1.9 (-9.3, 13.1) Internal passive rotation ROM:-8.9 (-18.8, 0.9) External passive rotation ROM:-0.1 (-13.3, 13.2) ND shoulder rotation test: 4 (n/a) ND shoulder flexion test:-1 (n/a) ND apprehension test: 2 (n/a) ND relocation test: 3 (n/a) ND release test: 2 (n/a) ND load shift anterior:-3 (n/a) ND load shift posterior: 0 (n/a)

				ND sulcus sign 2 cm: 0 (n/a) ND Gagey test: 3 (n/a) ND Rotés Queról test: 4 (n/a)
Luder et al. (2021)	Week 12	EX: SF-36: 1.74 (-3.76; 7.25) CO: SF-36:- 1.67 (-8.97; 5.63) EX: AIMS-2:-0.39 (-0.75;-0.03) CO: AIMS-2: 0 (-0.27; 0.27)	EX: MVC knee extensors: 0.006 N/bm (-0.034; 0.046) CO: MVC knee extensors: 0.011 N/bm (-0.017; 0.038) EX: RFD knee extensors: -0.178 N/s/bm (-0.563; 0.208) CO: RFD knee extensors:-0.280 N/s/bm (-0.657; 0.098) EX: MVC knee flexors: 0.007 N/bm (-0.033; 0.047) CO: MVC knee flexors: 0.033 N/bm (0.002; 0.065) EX: RFD knee flexors:-0.264 N/s/bm (-0.522;-0.007) CO: RFD knee flexors:-0.125 N/s/bm (-0.357; 0.107)	
Liaghat et al. (2022)	Week 16	EX: worst VAS10:-1.6 (n/a)** CO: worst VAS10:-2.5 (n/a)** EX-CO: worst VAS10 :-0.3 (-1.0; 0.4)** EX: best VAS10:-1.3 (n/a)** CO: best VAS10:-1.1 (n/a)** EX-CO: best VAS10:-1.0 (-2.0; 0.1)** EX: average VAS10:-2.2 (n/a)** CO: average VAS10:-1.8 (n/a)** EX-CO: average VAS10:-0.5 (-1.5; 0.5)**	EX: MVC scaption: 0.7 Nm/kg (n/a)** CO: MVC scaption: 0.03 Nm/kg (n/a)** EX-CO: MVC scaption: 0.05 Nm/kg (-0.04; 0.13)** EX: MVC internal rotation: 0.03 Nm/kg (n/a)** CO: MVC internal rotation: 0.04 Nm/kg (n/a)** EX-CO: MVC internal rotation: 0 Nm/kg (-0.07; 0.07)** EX: MVC external rotation: 0.03 Nm/kg (n/a)** CO: MVC external rotation: 0 Nm/kg (n/a)** EX-CO: MVC external rotation: 0.03 Nm/kg (-0.03; 0.08)**	EX: internal active rotation ROM: 71.2 (66.8; 75.7)** EX: external active rotation ROM: 107.0 (100.5; 113.6)** EX: internal passive rotation ROM: 69.9 (64.7; 75.2)** EX: external passive rotation ROM: 107.6 (100.0; 115.1)** CO: internal active rotation ROM: 68.9 (64.1; 73.7)** CO: external active rotation ROM: 100.6 (93.2; 108.1)** CO: internal passive rotation ROM: 72.6 (67.3; 78.0)** CO: external passive rotation ROM: 105.3 (96.9; 113.7)** EX-CO: internal active rotation ROM: 4.0 (−4.2; 12.2)** EX-CO: external active rotation ROM: 3.4 (−10.8; 17.5)** EX-CO: internal passive rotation ROM: −0.6 (−11.3; 10.2)** EX-CO: external passive rotation ROM: −0.5 (−16.4; 15.4)** EX: shoulder flexion test: 62 (47; 76)** CO: shoulder flexion test: 78 (64; 91)** Shoulder flexion test OR: 0.40 (0.09; 1.75)** EX: shoulder rotation test: 42 (28; 56)** CO: shoulder rotation test: 62 (47; 76)** Shoulder rotation test OR: 0.32 (0.13; 0.80)** EX: apprehension test: 62 (48; 76)** CO: apprehension test: 70 (55; 85)** Apprehension test OR: 0.59 (0.31; 1.13)** EX: relocation test: 44 (30; 58)** CO: relocation test: 55 (38; 72)** Relocation test OR: 0.59 (0.33; 1.08)** EX: release test: 37 (23; 51)**

				CO: release test: 50 (32; 68)** Release test OR: 0.58 (0.25; 1.35)** EX: load and shift anterior: 62 (47; 77)** CO: load and shift anterior: 68 (52; 84)** Load and shift anterior OR: 0.56 (0.23; 1.40)** EX: load and shift posterior: 18 (7; 29)** CO: load and shift posterior: 28 (13; 44)** Load and shift posterior OR: 0.63 (0.19; 2.04)** EX: sulcus sign 1 cm: 85 (70; 93)** CO: sulcus sign 1 cm: 84 (68; 93)** Sulcus sign 1 cm OR: 1.05 (0.28; 3.94)** EX: Gagey test: 90 (78; 100)** CO: Gagey test: 92 (85; 100)** Gagey test OR: 0.43 (0.14; 1.37)** EX: Rotés Queról test: 55 (41; 69)** CO: Rotés Queról test: 63 (48; 77)** Rotés Queról test OR: 0.72 (0.20; 2.66)**
Hakimi et al. (2023)	Week 9 (t9), week 15 (t15) and week 35 (t35)	EX: worst BPI (t9):-0.2 (n/a) CO: worst BPI (t9):-0.1 (n/a) EX: least BPI (t9):-0.5 (n/a) CO: least BPI (t9):-0.4 (n/a) EX: average BPI (t9):-0.7 (n/a) CO: average BPI (t9):-0.4 (n/a) EX: immediate BPI (t9):-0.2 (n/a) CO: immediate BPI (t9):-0.4 (n/a) EX: interference BPI (t9):-0.8 (n/a) CO: interference BPI (t9): 0.2 (n/a) EX: worst BPI (t15):-0.7 (n/a) EX: least BPI (t15):-0.7 (n/a) EX: average BPI (t15):-1.3 (n/a) EX: immediate BPI (t15):-0.1 (n/a) EX: interference BPI (t15):-1.4 (n/a) EX: worst BPI (t35):-0.2 (n/a) EX: least BPI (t35):-0.7 (n/a) EX: average BPI (t35):-0.6 (n/a) EX: immediate BPI (t35):-0.6 (n/a) EX: interference BPI (t35):-1.0 (n/a)	EX: 6MWT (t9): 70 m (n/a) CO: 6MWT (t9): 13 m (n/a) EX: 6MWT (t15): 43 m (n/a) EX: 6MWT (t35): 51 m (n/a)	

*Adjusted values and median difference (MedD) extracted when available; **post-intervention values only as pre-post differences not available; Not available (n/a); Experimental group (EX); Control group (CO); Experimental group minus control group (EX-CO); Maximum voluntary contraction strength (MVC); Rate of force development (RFD); Quadricep (QUAD); Hamstring (HAM); Numeric rating scale (NRS) from 0 (no pain) to 10 (worse pain); The distance (meters [m]) walked over 6 minutes (6-minute walking test [6MWT]); Medical Outcome Study Short Form–36 items (SF-36) assesses health-related QOL and functioning through physical and social functioning, role limitations, vitality, emotional well-being, pain and overall health scored from 0 (impaired) to 100 (unimpaired); Visual analogue scale from 0 (no pain) to 10 (extreme pain) (VAS10); Arthritis Impact Measurement Scales 2 (AIMS-2) measures physical, mental, social, emotional and occupational health status to provide a rating on a 0 to 10 scale, where 0 is optimal; McGill's trunk muscle endurance tests for the trunk flexor (FLEX), back extensor (EXT), and right lateral trunk musculature (rLAT) and left lateral trunk musculature (lLAT)

where isometric postures are maintained for time in seconds (s); ROM: range of motion; Rotés Queról test is positive when the shoulder goes beyond 90°; Gagey test when shoulder abduction exceeds 105 °; Sulcus sign is positive when the subacromial space is over a certain length; Load and shift test is positive if the glenoid head is farther than the glenoid (2 or 3, out of 0-3); Release test is positive if pain or apprehension appears following the release of the pressure on the glenohumeral joint; relocation test is positive when a patient reports apprehension or pain following posterior-directed force to the shoulder; Apprehension test is positive when a patient reports apprehension or pain following external rotation force to the shoulder; Shoulder rotation test is positive when the shoulder rotates beyond 180°; Shoulder flexion test is positive when the humerus is rested on the table following passive flexion; OR: Odds ratio; ND: number of participants pre- minus post-intervention; BPI: Brief Pain Inventory assesses pain severity and interference with daily living from 0 (insignificant pain/interference) to 10 (significant pain/interference).

2.4.3 Pain

One of the most common complains in people with hEDS/G-HSD is pain, which has a prevalence of up to 100%.[39,41] Inflammatory, nociceptive and neuropathic pain in both the joints and limbs have been reported in hEDS/G-HSD and is rated as severe.[42] It has been considered an important determinant of disability in people with hEDS/G-HSD.[43] Pain has been reported to stem from mechanical musculoskeletal changes, joint overuse, impaired proprioception, muscle weakness and central sensitization.[32,41] PA, notably consisting of stabilization and proprioceptive work, can mitigate pain by reducing the risk of injury and improving muscle strength, endurance and stability, motor control, body awareness, balance and posture.[1,32,34–36]

Trialed low-resistance programs seemed to improve general pain scores as well as pain scores during rest and movement in people with hEDS/G-HSD (Table 2.2).[15,23,26,27,29,30] Likewise, when assessing worst, least and average pain, and pain interference at week 9, 15 and 35, pain scores were decreased.[23] When the differences were compared to a control group, frequently the intervention group had a bigger difference.[15,23,26,27,29] Likewise, high-resistance programs reduce the average, best and worst pain levels following a rehabilitation intervention.[15,17,22] Only one trial compared the intervention to a control group and observe a slight improvement in the treatment versus no-treatment group.[17] Overall, these results suggest that pain can be mitigated by adhering to a low-resistance and high-resistance PA program.

2.4.4 Functional Capabilities and Disability

Physical and psychological disabilities are common in hEDS and often prevent participation in daily activities.[13,19] Patients report difficulty maintaining their usual daily functions, social life, attending school and tending to their occupations.[19] Consequently, some individuals with hEDS and G-HSD may be required to rely on others to complete unmanageable tasks.[19] PA, notably functional exercises that carry over to daily activities, can mitigate this burden and delay or reverse disability.[44]

Disability was assessed with various measures all evaluating disability and function slightly differently (Table 2.3). Physical and mental disability were reduced when evaluating a light-resistance programs.[23,30] Pre-post differences between physical and symptomatic outcomes were generally more pronounced than emotional, social or mental functions, especially when compared to a control group.[26,29] Activity performance and performance satisfaction also improved.[28]

High-resistance programs lightly suggest a benefit in functional capacities and disability[15,22]; however there are inconsistencies between measurement tools. One study showed a marked difference between the light- and high-resistance groups in the Western Ontario Shoulder Instability Index, while the Patient-Specific Functional Scale, Dartmouth Primary Care Cooperative Research Network/World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians chart, and European Quality of life and visual analogue scale scores had insignificant between-group differences.[22]

2.4.5 Proprioception and Balance

Coordination, balance and proprioception are diminished in people with hEDS/G-HSD compared to controls.[6,13,15,17] Strengthening and proprioceptive work is emphasized and is considered the most successful therapy for balance and proprioception.[36,45]

In light-resistance programs, angle error value decreased in the studies, signifying better proprioception following the interventions (Table 2.3).[15,26,29,30] Control groups habitually had no significant change or worse proprioception.[26,29,30] Balance was generally assessed using a static or dynamic balance board in either eyes open or eyes closed positions.[23,27,30] In all cases, balance improved, but not all were significant;[23,27,30] differences between the control and intervention groups were significant in eyes open in Toprak Celeney et al. (2017).[27] In Hakimi et al. (2023), improvement were larger following the intervention period than the control period during both eyes open and closed measures.[23]

Two studies assessed proprioception in the high-resistance trials using angle error values in low and middle ranges.[15,22] Decreased proprioception was observed in Liaghat et al. (2022) while Liaghat et al. (2020) demonstrated better proprioception following the interventions.[15,22] In the latter study, high-range proprioception worsened.[22] No heavy-resistance program assessed balance. Current evidence suggest at low-resistance exercises can improve balance, and that this type of program may be more favorable for proprioception improvements compared to a higher resistance approach.

2.4.6 Fatigue

Fatigue is present in over 80% of hEDS/G-HSD cases and can be severely disabling.[32] In fact, it is among the primary predictors of disability in people with hEDS/G-HSD.[43] Some of the most significant contributing factors are self-efficacy difficulties, pain, muscle weakness and respiratory insufficiency but extend to sleep disturbances, concentration problems, social functioning dysautonomia,[38] malabsorption, depression or anxiety disorder or use of analgesics.[46,47]

Fatigue was assessed in three studies, two of which were heavy-resistance programs, and one had a light-resistance comparator group (Table 2.3).[15,22] Improvements were seen in both the high-resistance groups and low-resistance group, with no significant between-group differences in fatigue scores post-treatment.[15,22] In a light-resistance rehabilitation trial, the total, general, mental and physical fatigue as well as reduced activity and motivation resulting from fatigue decreased from baseline for both the control and experimental periods at all timepoints;[23] however, the results from the latter were more pronounced than in the former.[23]

2.4.7 Kinesiophobia

Kinesiophobia – a fear of movement due to injury vulnerability – is highly apparent in people with hEDS/G-HSD and can lead to deconditioning.[13,43] In a study evaluating the correlates with kinesiophobia in hEDS/G-HSD, it was found that 93% of respondents had scores indicating severe kinesiophobia.[43] This fear has been reported in people with hEDS/G-HSD during mundane activities such as bathing, stair navigation and walking.[40] Coupled with other physical and

psychological symptoms, kinesiophobia can lead to deconditioning and a higher risk of injury as well as promote activity avoidance, disability and poor quality of life (QOL).[43,48,49]

In light-resistance PA interventions, kinesiophobia decreased (Table 2.3).[24,28] In Hakimi et al. (2023), kinesiophobia slightly increased following the control period, but decreased at every timepoint following the experimental period.[23] Spanhove et al. (2022) actually found that a larger mean difference was observed in the standard light-resistance program compared to the experimental program.[24] Post high-resistance programs, kinesiophobia scores were reduced,[15,22] with the study comparing the high- and low-resistance groups demonstrating a larger decrease in the higher resistant group. [15]

Table 2.3 Functional, Balance, Proprioception, Fatigue and Kinesiophobia Outcomes of Trials

Study	Timepoints	Outcomes: MD (95% CI)*			
		Functional Capabilities/Disability	Balance/Proprioception	Fatigue	Kinesiophobia
Ferrell et al. (2004)	Week 8	SF-36 physical functioning: 9.1 (n/a) SF-36 mental health: 27.8 (n/a)	BB (time out of balance): -1.35 s (n/a) AEV:-0.28° (n/a)		
Sahin et al. (2008)	Week 8	EX: AIMS-2 physical: -0.37 (n/a) CO: AIMS-2 physical:-0.04 (n/a) EX: AIMS-2 emotional:-0.30 (n/a) CO: AIMS-2 emotional: 0.33 (n/a) EX: AIMS-2 symptoms:-1.17 (n/a) CO: AIMS-2 symptoms:-0.90 (n/a) EX: AIMS-2 social: -0.06 (n/a) CO: AIMS-2 social: -0.08 (n/a) EX: AIMS-2 occupation:-1.84 (n/a) CO: AIMS-2 occupation:-0.92 (n/a)	EX: AEV (right): -0.90° (n/a) CO: AEV (right): 0.03° (n/a) EX: AEV (left): -0.79° (n/a) CO: AEV (left): 0.01° (n/a)		
Bathen et al. (2013)	Week 14 ½	COPM activity performance MedD: 1.13 (n/a) COPM performance satisfaction MedD: 2.15 (n/a)			TSK-13 MedD: -4 (n/a)
Toprak Celenay et al. (2017)	Week 8		EX: MedD sBB eyes closed:-0.5 (-3.1; 1.6) CO: MedD sBB eyes closed:-0.3 (-1.8; 1.0) EX: MedD mBB eyes closed:-1.3 (-6.3; 2.2) CO: MedD mBB eyes closed: 0.0 (-3.3; 3.6) EX: MedD sBB eyes open:-0.3 (-3.5; 1.5) CO: MedD sBB eyes open:-0.4 (-2.1; 1.6) EX: MedD mBB eyes open:-0.1 (-1.2; 0.8) CO: MedD mBB eyes open: 0.1 (-1.5; 1.0)		
Daman et al. (2019)	Week 4	EX: SF-36 physical functioning: 11.39 (n/a) CO: SF-36 physical functioning: 0.05 (n/a) EX: SF-36 mental health: 0.66 (n/a) CO: SF-36 mental health: 0.76 (n/a)	EX: weight-bearing AEV: -3.71 (n/a) CO: weight-bearing AEV: 0.07 (n/a) EX: non-weight-bearing AEV: -1.77 (n/a) CO: non-weight-bearing AEV: 0.12 (n/a)		
Liaghat et al. (2020)	Week 16	WOSI: -528 (-738;-318) EQ-5D-3L: 0.01 (-0.08; 0.09) EQ-VAS: 7 (-7; 21) COOP/WONCA: -1.2 (-4.5; 2.1)	AEV low range:-1.2° (-2.4; 0.0) AEV mid range: -0.9° (-2.2; 0.3) AEV high range: 0.6° (-2.0; 3.2)	CIS:-9 (-16;-2)	TSK-11: -3.3 (-5.7;-0.8)

Luder et al. (2021)	Week 12	EX: SF-36 physical functioning: -0.36 (-2.04; 1.31) CO: SF-36 physical functioning: -0.41 (-1.93; 1.11) EX: SF-36 mental health: 0.54 (-3.95; 2.87) CO: SF-36 mental health: 2.05 (-0.01; 4.11) EX: AIMS-2 total: -1.59 (-3.82; 0.64) CO: AIMS-2 total: -1.82 (-3.73; 0.08)			
Spanhove et al. (2022)	Week 6 (t6), week 12 (t12), and week 24 (t24)	EX: DASH (t24): -10 (n/a) CO: DASH (t24): -10 (n/a) EX+CO: DASH (t24):-8.6 (-2.4;-14.8) EX: WOSI (t24): -460 (n/a) CO: WOSI (t24):-278 (n/a) EX+CO: WOSI (t12):-240 (-27.6;-452.8) EX+CO: WOSI (t24): -325 (-112;-538) EX: PSFS (t24): 4 (n/a) CO: PSFS (t24): 5 (n/a) EX+CO PSFS: 4.3 (0.75; 7.95) EX: GROC (t24 from t6): 0.85 (n/a) CO: GROC (t24 from t6): 1.26 (n/a) EX+CO: GROC (t24 from t6): 1.02 (0.36; 1.67)			EX: TSK-17 (t24): -1.5 (n/a) CO: TSK-17 (t24): -2.5 (n/a)
Liaghat et al. (2022)	Week 16	EX: WOSI:-435.2 (n/a) CO: WOSI:-268.9 (n/a) EX-CO: WOSI: -174.5 (-341.4;-7.7) EX: PSFS: 1.8 (n/a)** CO: PSFS: 1.7 (n/a)** EX-CO: PSFS: 0.2 (-1.0; 1.4)** EX: COOP/WONCA:-1 (n/a)** CO: COOP/WONCA:-1 (n/a)** EX-CO: COOP/WONCA:-0.5 (-2.2; 1.2) EX: EQ-5D-5L: 0.08 (n/a)** CO: EQ-5D-5L: 0.09 (n/a)** EX-CO: EQ-5D-5L: 0.02 (-0.02; 0.07)** EX: EQ-VAS: 4.9 (n/a)** CO: EQ-VAS: 10.7 (n/a)** EX-CO: EQ-VAS : 0.3 (-8.0; 8.6)**	EX: AEV low range: 0.58° (n/a)** CO: AEV low range:-0.45° (n/a)** EX-CO: AEV low range: 0.65° (-1.60; 2.90)** EX: AEV mid range: 0.61° (n/a)** CO: AEV mid range:-0.76° (n/a)** EX-CO: AEV mid range: 1.17° (-0.27; 2.60)**	EX: CIS:-7.1 (n/a)** CO: CIS:-4.7 (n/a)** EX-CO: CIS:-2.5 (-7.1; 2.2)**	EX: TSK-11:-1.6 (n/a)** CO: TSK-11:-1.2 (n/a)** EX-CO: TSK-11:-0.8 (-2.7; 1.1)**

Hakimi et al. (2023)	Week 9, week 15 (t15), and week 35 (t35)	EX: SF-36 physical functioning (t9): 1.5 (n/a) CO: SF-36 physical functioning (t9): 1.7 (n/a) EX: SF-36 physical functioning (t15): 4.7 (n/a) EX: SF-36 physical functioning (t35): 3.9 (n/a) EX: SF-36 mental health (t9): 6.3 (n/a) CO: SF-36 mental health (t9):-0.2 (n/a) EX: SF-36 mental health (t15): 7.5 (n/a) EX: SF-36 mental health (t35): 4.7 (n/a)	EX: CEA eyes open (t9):-178 mm^2 (n/a) CO: CEA eyes open (t9):-33 mm^2 (n/a) EX: CEA eyes open (t15):-136 mm^2 (n/a) EX: CEA eyes open (t35):-74 mm^2 (n/a) EX: SP eyes open (t9):-30 mm (n/a) CO: SP eyes open (t9):-12 mm (n/a) EX: SP eyes open (t15):-133 mm (n/a) EX: SP eyes open (t35):-72 mm (n/a) EX: CEA eyes closed (t9):-766 mm^2 (n/a) CO: CEA eyes closed (t9): 14 mm^2 (n/a) EX: CEA eyes closed (t15):-1,166 mm^2 (n/a) EX: CEA eyes closed (t35):-531 mm^2 (n/a) EX: SP eyes closed (t9):-154 mm (n/a) CO: SP eyes closed (t9): 125 mm (n/a) EX: SP eyes closed (t15):-429 mm (n/a) EX: SP eyes closed (t35):-197 mm (n/a)	EX: MFI general (t9):-1.4 (n/a) CO: MFI general (t9):-0.9 (n/a) EX: MFI general (t15):-1.9 (n/a) EX: MFI general (t35):-1.1 (n/a) EX: MFI physical (t9):-2.0 (n/a) CO: MFI physical (t9):-0.1 (n/a) EX: MFI physical (t15):-2.9 (n/a) EX: MFI physical (t35):-1.8 (n/a) EX: MFI mental (t9):-0.9 (n/a) CO: MFI mental (t9):-0.3(n/a) EX: MFI mental (t15):-1.6 (n/a) EX: MFI mental (t35):-0.8 (n/a) EX: MFI reduced activity (t9):-2.0 (n/a) CO: MFI reduced activity (t9):-0.5 (n/a) EX: MFI reduced activity (t15):-2.1 (n/a) EX: MFI reduced activity (t35):-2.1 (n/a) EX: MFI reduced motivation (t9):-1.4 (n/a) CO: MFI reduced motivation (t9):-0.2 (n/a) EX: MFI reduced motivation (t15):-1.5 (n/a) EX: MFI reduced motivation (t35):-0.7 (n/a) EX: MFI total (t9):-7.7 (n/a) CO: MFI total (t9):-1.4 (n/a) EX: MFI total (t15):-9.9 (n/a) EX: MFI total (t35):-6.4 (n/a)	EX: TSK-17 (t9):-2.4 (n/a) CO: TSK-17 (t9): 0.2 (n/a) EX: TSK-17 (t15): -1.9 (n/a) EX: TSK-17 (t35): -4.3 (n/a)

*Adjusted values and median difference (MedD) extracted when available; **post-intervention values only as pre-post differences not available; Not available (n/a); Experimental group (EX); Control group (CO); Experimental group minus control group (EX-CO); Experimental group combined with control group (EX+CO); Angle error value in degree (°)(AEV); Medical Outcome Study Short Form–36 items (SF-36) assesses health-related QOL and functioning through physical and social functioning, role limitations, vitality, emotional well-being, pain and overall health scored from 0 (impaired) to 100 (unimpaired). Scores can be summed into physical and mental health scores; Arthritis Impact Measurement Scales 2 (AIMS-2) measures physical, mental, social, emotional and occupational health status to provide a rating on a 0 to 10 scale, where 0 is optimal; A balance board (BB), static (sBB) and mobile (mBB) from which a stability index is given, where a high value indicates low stability; Western Ontario Shoulder Instability Index (WOSI) measured shoulder function from 0 (no limitations) to 2100 (extreme limitations); 30-item Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire assesses shoulder disability from 0 (no disability) to 100 (complete disability); Patient-Specific Functional Scale (PSFS) assesses function on 3 patient-important activities from 0 (unable to perform) to 10 (can perform unhelped); Global Rating of Change (GROC) assesses self-perceived improvement ranging from minus 5 (a lot worse) to 5 (a lot better); Checklist of Individual Strength (CIS), subscale of fatigue from 8 to 56, where 56 is the worst fatigue; Dartmouth Primary Care Cooperative Research Network/World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians (COOP/WONCA) assesses functional health status from 6 (good functional status) to 30 (poor functional status); European Quality of life -5 Dimensions -5-Level Scale (EQ-5D-5L) evaluates health-related quality of life from < 0 to 1 (full health); European Quality of life visual analogue scale (EQ-VAS) where the patient's current health is rated from 0 (worst imaginable health) to 100 (best imaginable health); Stabilimeter on a multi-axis motorized platform, where deviations from the center of pressure using a 95% confidence ellipse area (CEA) and the sway path (SP); Multidimensional Fatigue Inventory is a self-administered 1-to-5 questionnaire with 20 items with five dimensions: general fatigue (MFIg), physical fatigue (MFIp), mental fatigue (MFIm), reduced activity (MFIra) and reduced motivation (MFIrm), with a higher total score (MFIt) indicating significant fatigue.

2.5 PA Behaviours in hEDS/G-HSD

Two studies have reported on PA behaviours. Reychler et al. (2019) administered the Baecke PA Questionnaire which assess PA during occupational, sport and leisure activities within the previous 12 months ranging from three (not active) to 15 (very active), in 20 participants.[25] This study reported an overall Beacke PA score of 6.6.[25]

Simonds et al. developed a study to assess perceptions of PA within which they identified PA behaviours.[50] They summarized total weekly duration of physical activity categories (0, less than 30 minutes, 30-60 minutes, 60-150 minutes, over 150 minutes) and performed a multiple logistic regression with medical, sociodemographic and belief variables.[50] Overall, 10.7%, 15.6%, 20.8%, 26.6% and 26.2% perform physical activity for a duration of 0 minutes, less than 30 minutes, between 30 and 60 minutes, between 60 and 150 minutes and for over 150 minutes, respectively.[50] The study reported correlations between PA duration and employment, education, exercise advice from physiotherapists, various beliefs, poor balance, dizziness/fainting and fatigue, however did not address the impact of barriers.[50]

Most of the trialed rehabilitation programs are focused on muscle-strengthening; no study reports the duration of this type of PA, or of moderate and vigorous PA. Different types of PA have different benefits,[51] therefore it is important to understand the duration of all the PA types and the factors that influence each one. There is also a paucity of knowledge of the degree of influence of various barrier and facilitators, and their association with PA. This is crucial knowledge for developing an effective hEDS/G-HSD-specific intervention to increasing PA levels.[52,53] This information, coupled with the associations between PA and medical and sociodemographic variables, can truly inform who to target, what to target and how to target it.

2.6 Conclusion: What is Next?

The above trials demonstrate favourable results for various types muscle-strengthening exercise programs. Overall, joint laxity, instability, range of motion, pain, fatigue and kinesiophobia decreased, while muscle strength and endurance, functional abilities, proprioception and balance.

[15,17,22–30] This confirms that PA should be an ongoing recommendation for the management of hEDS/G-HSD symptoms. Despite the benefits of PA for hEDS/G-HSD symptoms, current research demonstrates low PA participation. Identifying people with hEDS/G-HSD's involvement in different PA types and what encourages and discourages participation can inform the development of an intervention aiming to improve PA uptake and maintenance. In turn, self-management of hEDS/G-HSD be facilitated, and wellness, ameliorated.

2.7 Supplementary Materials

Supplementary Materials 1: Search Strategy Example - Medline

“hypermobil*” AND (stair climbing/ or warm-up exercise/ or dancing/ or "play and playthings"/ or sports/ or exp athletic performance/ or exp martial arts/ or exp racquet sports/ or exp running/ or skating/ or exp snow sports/ or soccer/ or sports for persons with disabilities/ or exp swimming/ or "track and field"/ or volleyball/ or walking/ or weight lifting/ or wrestling/ or youth sports/ or exp Exercise/ or exp *Physical Education/ or (gymnasi* or intramural* or playground* or sedentary or inactiv* or "outdoor facilit*" or exercis* or MVPA or vpa or mva or pedometer* or accelerometer* or fitbit* or aerobics or aikido or athletics or archery or badminton or ballet or bandy or barre or "base jumping" or basketball or biathlon or billiards or bobsleigh or bocce or "body building" or bouldering or boules or bowling or boxing or broomball or calesthentic* or cammag or camogie or "circuit training" or climbing or cricket or curling or cycling or dance or dances or dancing or discus or diving or fencing or football or futbol or gardening or golf or gymnastic* or handball or "hammer throw*" or "hang gliding" or "hip hop" or hockey or "horseback rid*" or hurling or javelin or jogging or judo or "jiu jitsu" or karate or kayaking or kickbox* or kiteboarding or "kung fu" or lacrosse or "lawn bowl*" or longboarding or luge or marathon* or "martial arts" or mountaineering or orienteering or paddling or parkour or pickleball or polo or powerlifting or qigong or racewalking or "racquet ball" or raquetball or ringette or rowing or rugby or running or sailiing or shinty or skate or skateboarding or skating or snooker or snorkelling or snowshoe* or soccer or sport* or swim* or tai-kwan-do or taekwondo or "tai chi" or telemark or tennis or tobogganing or (track adj2 field) or triathlon or "ultimate frisbee" or ultramarathon* or volleyball or walking or weight lifting or weightlifting or windsurfing or wrestling or wushu or yoga).mp. or (physical* adj2 (activ* or educat* or training or curricul* or literacy or compulsory or mandatory or daily)) or (activit* adj2 (track or record)) or (fitness adj2 (training or class* or program* or activit*)).mp)

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3.0 CHAPTER 3: Physical Activity Behaviours, Barriers and Facilitators in Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorder

3.1 Introduction

Generalized Hypermobility Spectrum Disorder (G-HSD) and Hypermobile Ehlers-Danlos Syndrome (hEDS) are two connective tissue disorders characterized by symptomatic generalized joint hypermobility.[1,2] The combined prevalence of hEDS and G-HSD is estimated to be between five to eight out of 5,000, with a higher prevalence in women than in men. [3–5]

Experts have placed G-HSD and hEDS on the same clinical spectrum as they both result in hypermobility-induced musculoskeletal manifestations and share similar phenotypes.[6,7] People with G-HSD or hEDS (G-HSD/hEDS) frequently experience joint instability, reoccurring injuries chronic pain, skin laxity and fragility, fatigue, headaches and migraines, psychiatric disorders as well as gastrointestinal, pelvic, gynecological and autonomic dysfunction.[3] These occurrences have been associated with low quality of life, reduced participation in activities of daily living and disability. [1,3,8]

Symptom management is at the core of well-being in people with hEDS/G-HSD. Physical activity (PA) is considered one of the most effective self-management tools for generalized joint hypermobility.[1,9–11] PA has been shown to improve muscle strength, endurance, functional abilities, proprioception and balance, as well as reduce pain, fatigue, kinesiophobia and disability.[1,2,4,11–14] However, there are currently no widely accepted evidence-based PA program for individuals with hEDS/G-HSD. While there is no doubt on the benefits of PA on people with hEDS/G-HSD, it is reported that barely half participate in over an hour of PA per week, which is well below the national Canadian Movement Guidelines recommendations.[15] Many factors, including education, employment status, beliefs about PA and symptoms, may determine the uptake and adherence to PA.[16]

There is currently a gap in the literature of the duration and types of different PAs performed by people with hEDS/G-HSD. Furthermore, no study has reported the influence of a broad spectrum

of barriers and facilitators on PA participation in this population. The latter is important to identify the primary determinants of PA uptake and maintenance. These are important gaps to fill as PA has the potential to alleviate the impact of these disorders and increase the overall health of this population. Hence, this study sets out to identify the current physical activity behaviours in terms of muscle-strengthening, vigorous and moderate PA, walking and stretching/foam rolling of Canadian adults with hEDS/G-HSD, and assess the associations between various barriers and facilitators of PA.

3.2 Methods

3.2.1 Participants

Canadians aged 18 years old and over self-reporting a diagnosis of hEDS or G-HSD by a medical provider were invited to participate in the online survey. Recruitment took place from January 28th, 2023, to March 31st, 2023 via patient support groups on Facebook, newsletters through The Improving the Lives of Children (ILC) Foundation and *Le regroupement Québécois des maladies orphelines*, as well as pamphlets set out at a rehabilitation clinic in Victoria, Canada.

3.2.2 Questionnaire

Participants completed an anonymous questionnaire (Supplementary Materials 1, Figure S3.1) hosted on the REDcap platform.[17,18] The questionnaire had four sections. The first part was on medical history: age, diagnoses in addition to hEDS/G-HSD, symptoms, life stage at symptom and flare-ups. The diagnoses and symptoms listed on the questionnaire are those most reported in hEDS/G-HSD[19] that have the potential to prevent PA.[16] Pain (Defense and Veterans Pain Rating Scale [DVPS])[20], kinesiophobia (Tampa Kinesiophobia Scale 4-item [TKS-4])[21], gastrointestinal symptoms (Numeric Rating Scale [NRS])[22,23] and fatigue (NRS)[22,24] were assessed. The DVPS is a scale from 0-10 that describes the interference of pain in daily life, where mild, moderate and severe pain are from 1-4, 5-6 and 7-10, respectively.[20] The TKS-4 is a measure of kinesiophobia which contains 4 components; it is scored from no catastrophic thinking, 4, to maximum catastrophic thinking, 16, with a definite threshold of experiencing kinesiophobia at a score of 8.[21,25] The NRS is a 0 to 10 scale where fatigue and gastrointestinal symptoms' scores between 1

and 3, 4 and 6, and 7 and 10 are rated as mild, moderate and severe, respectively.[26,27] Details on the validity and reliability of the questionnaires can be found in Supplementary Materials 1.

The second section collected sociodemographic information: cultural background, gender, marital status, education and employment status by adopting sociodemographic survey question formulations by Statistics Canada.[28–30] The third asked participants to describe their weekly vigorous, moderate and muscle-strengthening PA as well as walking, stretching and sedentary behaviors using the International Physical Activity Questionnaire – Short Form (IPAQ-SF).[31]

Lastly, the remaining section pertained to describing the barriers and facilitators to PA using the Inflammatory Arthritis Facilitators and Barriers (IFAB) questionnaire.[32] It evaluates the degree on a scale of 0 to 10, to which participants' see symptoms, weather, social and medical support, access to facilities, motivation, time, beliefs and knowledge of PA as barriers or facilitators to participating in PA, for a total ranging between -120 and 50 where negative scores signify a higher presence of barriers.[32] Supplement 1 contains information on validity and reliability of the DVPS, TKS-4, NRS, IPAQ-SF and IFAB. A section for participants to describe any other factors that influence PA behaviors was added to the questionnaire. The contents of the questionnaire received input from a patient with hEDS and an academic chairing a Canadian Ehlers-Danlos Syndrome organization. This study was approved by the University of Alberta Ethics Committee (Pro00124933).

3.2.3 Data Analysis

Medical and sociodemographic information as well as IPAD-SF- and IFAB-based close-ended questions were analyzed using complete case data. Descriptive analyses were conducted by diagnosis group where inter-group differences of categorical and medians of continuous variables were tested using Pearson's chi2 at a significance level of 0.05. Median (interquartile range [IQR]) and frequency (percentage [%]) were used to describe continuous variables and categorical variables, respectively. The responses received from open-ended questions (i.e., reason for flare-ups, types of PAs) and responses derived from the "other" field for multiple-choice questions were

grouped using content analysis, consisting of inductive coding, by one person (AH) with previous experience in thematic analysis.[33]

Regression models were used for explanatory purposes. Candidate variables derived from the questionnaire (Supplementary Materials 2) and hypothesized interaction terms with a minimum univariate analysis p-value of 0.20 with the outcome were considered for modeling. A hypothesis-driven strategy[34] with a model retention p-value of 0.15 was used to build four models for which the total IFAB score was the independent variable of interest using a backwards stepwise approach. Duration of muscle-strengthening and moderate PA was summed; both measures were used as outcomes in multivariable regression analyses. Two logistic regressions were conceived with the following outcomes: participation in vigorous PA and meeting the Canadian Movement Guidelines. The former was defined as doing at least 10 minutes of vigorous physical activity, while the latter was defined as a minimum of 150 minutes of moderate and/or vigorous PA and at least two days of muscle-strengthening activities in a typical week. Confounding variables were retained in the model, and model assumptions were examined. Influential observations were assessed using dfbeta, Cook's distance, studentized residual plot and leverage. Data was analyzed using STATA version 17.[35]

3.3 Results

3.3.1 Sample Characteristics

One hundred and eighty-eight surveys were completed and submitted. Two observations were removed due to a high likelihood of record duplication. Descriptive analyses were primarily conducted by diagnosis group (Supplementary Materials 3). Of the 186 respondents, one hundred and forty-three (76.9%) participants were diagnosed with hEDS compared to 42 (22.6%) with G-HSD. The prevalence of postural orthostatic tachycardia syndrome, mast cell activation syndrome and the inability to work were significantly higher in those with hEDS compared to G-HSD (59.4% vs. 38.1%; 49.0% vs. 31.0%; 37.1% vs. 19.1%, respectively). Likewise, significant differences were noted by diagnosis provider (p-value: <0.01). Despite these differences, similarities among groups were strong (Supplementary Materials 3); therefore, data were summarized pooling both

diagnosis groups together. One hundred and sixty-four (88.0%), 17 (9.1%) and four (2.2%) participants identified as a woman, non-binary person, man, respectively. The median age was 42 years old with participant age ranging from 19 to 76 years old. Inability to work was high, at a prevalence of 61 (32.8%).

Pain, fatigue and gastrointestinal dysfunction were prevalent. They were reported in 184 (98.9%), 174 (93.6%) and 163 (87.6%) individuals, respectively. Fatigue was severe with a median NRS score of 7 (IQR = 2). The pain and gastrointestinal scores were moderate, with a median rating of 6 (IQR = 2) and 5 (IQR = 4), respectively. The median TSK-4 score was 11, demonstrating the presence of kinesiophobia in the study sample.[25] Table 3.1 and 3.2 describe the sample's sociodemographic and medical characteristics, respectively.

Table 3.1 Sociodemographic Characteristics (n = 186)

Characteristics		*Frequency (%)*
Age		
	18-29 years	39 (21.0)
	30-39 years	40 (21.5)
	40-49 years	63 (33.9)
	50-59 years	22 (11.8)
	60+ years	17 (9.1)
	Median (IQR[a])	42 (17)
	Missing	5 (2.7)
Gender		
	Woman	164 (88.2)
	Non-binary	17 (9.1)
	Man	4 (2.2)
	Missing	1 (0.5)
Ethnicity[b]		
	European	146 (78.5)
	North American	65 (35.0)
	Aboriginal	8 (4.3)
	Asian	7 (3.8)
	African	6 (3.2)
	Central-South American	3 (1.6)
	South-Est Asian	2 (1.1)
	Missing	6 (3.2)
Province of residence		
	Ontario	73 (39.3)
	British Columbia	39 (21.0)
	Prairies	37 (19.9)
	Quebec	17 (9.1)
	Maritimes/Newfoundland and Labrador	11 (5.9)

	Yukon	1 (0.5)
	Missing	8 (4.3)
Education		
	University or higher degree	77 (41.4)
	College/CEGEP degree	59 (31.7)
	High school degree	33 (17.7)
	Less than a high school degree	2 (1.1)
	Missing	15 (8.1)
Work status[b]		
	Unable to work	61 (32.8)
	Full-time	52 (28.0)
	Part-time	33 (17.7)
	Self-employed	23 (12.4)
	Student	21 (11.3)
	Unemployed	15 (8.1)
	Homemaker	10 (5.4)
	Retired	8 (4.3)
	Missing	0 (0.0)

[a] interquartile range; [b] participants could check multiple options.

Table 3.2 Medical Characteristics (n = 186)

Characteristics		*Descriptive Statistic*
Diagnosis (n [%])		
	hEDS	143 (76.9)
	G-HSD	42 (22.6)
	Missing	1 (0.5)
Start period (n [%])		
	Childhood	100 (53.8)
	Adolescence	36 (19.4)
	Infancy	23 (12.4)
	20-29 years old	13 (7.0)
	30+ years old	11 (5.9)
	Missing	3 (1.6)
Diagnosis provider (n [%])		
	Geneticist	80 (43.0)
	Rheumatologist	40 (21.5)
	Family physician/pediatrician/internist	31 (16.7)
	Physiatrist/orthopedist/pain specialist	28 (15.1)
	Other	5 (2.7)
	Missing	2 (1.1)
Symptom occurrence (n [%])[a]		
	Pain	184 (98.9)
	Fatigue	174 (93.6)
	Subluxations/dislocations	173 (93.0)
	Gastrointestinal dysfunction	163 (87.6)
	Headaches/migraines	143 (76.9)
	Anxiety, depression or panic disorder	138 (74.2)
	Postural orthostatic tachycardia intolerance	101 (54.3)
	Pelvic floor and/or bladder dysfunction	100 (53.7)
	Severe menstrual cramps[b]	87 (53.1)
	Neurodivergent condition	93 (50.0)

Mast cell activation syndrome	83 (44.6)
Missing	0 (0.0)
Defense and Veterans Pain Rating Scale[c]	
Median (IQR[d])	6 (2)
Missing (n [%])	7 (3.8)
Gastrointestinal Numeric Rating Scale[c]	
Median (IQR)	5 (4)
Missing (n [%])	5 (2.7)
Fatigue Numeric Rating Scale[c]	
Median (IQR)	7 (2)
Missing (n [%])	1 (0.5)
Tampa Kinesiophobia Scale-4 Item total score[e]	
Median (IQR)	11 (4)
Missing (n [%])	5 (2.7)

[a] participants could check multiple options; [b] out of 164 women; [c] ranges from 0 to 10; [d] interquartile range; [e] measured by the Tampa Scale for Kinesiophobia Short Form which ranges from 4 to 14.

Mobility aids were never, sometimes and always used in 94 (51.4%), 75 (41.0%) and 14 (8.0%) of respondents, respectively. Cane (n = 56 [62.9%]) and braces (n = 52 [58.4%]) were most frequently used, followed by crutches (n = 23 [25.8%]), walking poles (n = 20 [22.5%]) and walkers (n = 20 [22.5%]). Mobility aids were primarily used for balance (n = 44 [49.4%]) and joint stability (n = 26 [29.2%]), and to mitigate pain (n = 57 [64.0%]), dizziness (n = 20 [22.5%]), subluxation/dislocation (n = 11 [12.4%]) and dysautonomia symptoms (n = 11 [12.4%]). Table S3.6 in Supplementary Materials 4 details the reasons for mobility aid use.

Ninety-eight (52.7%) respondents reported that they were undergoing a flare-up at the time of the survey. The median flare-up severity was 7 out of 10, with the most common causes being injury (n = 11 [11.2%]), stress (n = 9 [9.2%]), dislocations/subluxations (n = 9 [9.2%]) and weather (n = 9 [9.2%]). Pain, dislocations/subluxations, headaches/migraines, fatigue and gastrointestinal dysfunction were the most commonly experienced symptoms during flare-up, at a prevalence of 55 (56.1%), 20 (20.4%), 16 (16.3%), 15 (15.3%) and 13 (13.3%), respectively. Table S3.7 and S3.8 in Supplementary Materials 4 displays the flare-up symptoms experienced and causes.

3.3.2 Physical Activity Behaviours

PA, either vigorous, moderate, muscle-strengthening, walking or stretching/foam rolling were reported by all but 8 (4.3%) individuals. The median total duration of PA was 240 minutes per week. Vigorous, moderate and muscle-strengthening PA was undertaken for a median of 0, 120

and 10 minutes per week, respectively. Walking was performed most frequently (n = 166 [89.3%]) for a median of 210 (IQR = 330) minutes per week, and sitting and lying down were reported for a median of 540 (IQR = 480) minutes. The median duration of stretching/foam rolling was 0 minutes.

Table 3.3 summarizes the muscle-strengthening, moderate PA, vigorous PA and the proportion meeting the Canadian Movement Guidelines. Of the 63 (34.4%) respondents that participated in vigorous PA, walking, weightlifting, cycling and swimming were reportedly performed by 24 (38.1%), 17 (27.0%), 15 (23.8%) and 9 (14.3%) people, respectively. Dancing, running and aerobics were each undertaken by 7 participants. The most frequent moderate PA among the 137 (74.5%) participants were house and yardwork (n = 90 [65.7%]), walking (n = 46 [33.6%]), carrying loads (n = 39 [28.5%]), stair-climbing and-descending (16 [11.7%]) and cycling (n = 14 [10.2%]). Ninety-five (51.9%) people with hEDS/G-HSD participate in muscle-strengthening PA; weightlifting (39 [41.1%]), of which many specified lighter weights, was the most frequently reported. It was followed by resistance bands and cables, bodyweight exercises, physiotherapy exercises and pilates, at a frequency of 35 (36.8%), 34 (35.8%), 26 (27.4%) and 12 (12.6%), respectively. Table S3.9 through S3.12 in Supplementary Materials 4 lists the types of vigorous, moderate and muscle-strengthening PAs undertaken and their frequencies.

Table 3.3 Physical Activity Types, Frequency and Duration

Types of Physical Activity (median [IQR[a]])	Sample (n = 186)
Vigorous	
n (%)	63 (34.4)
Days per week[b]	0 (2)
Minutes per week[b]	0 (60)
Moderate	
n (%)	137 (74.5)
Days per week	2 (4)
Minutes per week	120 (300)
Muscle-strengthening	
n (%)	95 (51.9)
Days per week	1 (3)
Minutes per week	20 (112)
Meeting the Canadian Movement Guidelines	
n (%)	59 (31.7)

[a] Interquartile range; [b] out of entire sample.

3.3.3 Barriers and Facilitators to Physical Activity

Barriers and facilitators were assessed using the IFAB questionnaire. Symptoms were a barrier and had a median rating of -7.5. Pain (n = 133), fatigue (n = 85), subluxation/dislocation (n = 30) and dizziness/fainting (n = 29) were the most commonly reported influences on PA participation. Weather and a belief that PA makes symptoms worse were barriers with a median rating of -6. The strongest facilitators were support from friends and family, support from healthcare professionals and access to facilities (Table 3.4).

Table 3.4 Barriers and Facilitators to Physical Activity

	Rating (median [IQR])
Barriers or facilitators (-10 to 10)[a]	
Symptoms	-7.5 (3)
Weather	-6 (6)
Support from friends and family	5 (5)
Support from healthcare professionals	4 (6)
Access to facilities	4 (12)
Barriers (-10 to 0)[b]	
A belief that PA makes symptoms worse	-6 (6)
Lack of motivation	-5 (4)
Lack of time	-3.5 (6)
Lack of knowledge on which exercises to do, how much and how often	-3 (6)
Lack of knowledge of benefits of physical activity for general health and/or condition management	-1 (3)
Lack of knowledge of benefits of physical activity for mood	-1 (2)
Limited confidence on how to exercise safely	-5 (7)
Total IFAB[c] score	-28 (29)

[a] could be rated as a barrier (negative), facilitator (positive) or no impact; [b] could be rated as a barrier (negative) or no impact; [c] Inflammatory Arthritis Facilitators and Barriers questionnaire, ranging from -120 to 50.

Respondents listed other influential factors on PA participation in an open-ended question: access to hEDS/G-HSD-knowledgeable healthcare providers and the cost of PA were mentioned by 12 (6.5%) and 10 (5.4%) people, respectively. Regular access to healthcare providers and cost of healthcare were listed 6 (3.2%) times. Table S3.13 in Supplementary Materials 4 lists all the other barriers and facilitators.

Table 3.5 Outcomes of Regression Analyses

	Probability of meeting the Canadian Movement Guidelines (yes/no)		Probability of participating in vigorous PA in a typical week (yes/no)		Duration of moderate PA per week (minutes)		Duration of muscle-strengthening PA per week (minutes)	
Pseudo R2	0.17		0.25		—		—	
Adjusted R2	—		—		0.11		0.14	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value	Coefficient (95% CI)	p-value	Coefficient (95% CI)	p-value
Total IFAB score[a]	1.04 (1.02; 1.06)	<0.01	1.02 (1.01; 1.04)	0.01	3.67 (0.37; 6.98)	0.03	1.19 (0.60; 1.79)	<0.01
Unable to work								
Yes	0.13 (0.05; 0.37)	<0.01	0.13 (0.05; 0.38)	<0.01	-264.26 (-414.42; -114.11)	<0.01		
No (ref[b])	—	—	—	—	—	—		
Presence of severe menstrual cramps								
Yes							26.98 (-0.82; 54.78)	0.06
No (ref)							—	—
Use of support aids								
Sometimes/always			0.49 (0.23; 1.02)	0.06			-39.64 (-66.75; -12.54)	<0.01
Never (ref)			—	—			—	—
Gender								
Man or non-binary[c]							36.33 (-8.27; 80.93)	0.11
Woman (ref)							—	—
Age								0.10
60+							-61.90 (-111.63; -12.17)	
50-59							-14.73 (-53.95; 24.50)	
40-49							-33.22 (-75.10; 8.66)	
30-39							-3.38 (-58.95; 52.19)	
18-29 (ref)							—	
Gastrointestinal discomfort score[d]					36.88 (6.04; 67.73)	0.02		
Pain score[d]			0.70 (0.53; 0.91)	<0.01				
Presence of postural orthostatic tachycardia symptoms								
Yes					138.05 (-1.21; 277.32)	0.05		
No (ref)					—	—		
Education						0.02		
University or higher					-249.90 (-445.25; -54.56)			
College/CEGEP					-72.64 (-274.87; 129.58)			
Highschool or less (ref)					—			
North American ethnicity								
Yes			2.25 (1.05; 4.82)	0.04				
No (ref)			—	—				

[a]Inflammatory Arthritis Facilitators and Barriers questionnaire from -120 to 50; [b] reference group; [c] combined as a result of small sample sizes to be compared to women; [d] measured using the numeric rating scale which ranges from 0 (none) to 10 (most severe).

Significant univariate associations for each outcome are in Supplementary Materials 5. Logistic and linear regression results are summarized in Table 3.5. One outlier was removed in each of the muscle-strengthening and moderate PA models. One observation was removed in the moderate and vigorous PA models due to the sole inclusion of walking in both these PA types, and omitting their walking duration in the walking section. Adjusted and pseudo-R-squared values were low for all models (≤0.25). IFAB score was positively associated with duration of muscle-strengthening activities and moderate PA as well as participating in vigorous PA and meeting the Canadian Movement Guidelines.

Ability to work was a strong predictor for duration of moderate, and probability of participating in vigorous PA and meeting the Canadian Movement Guidelines; participants that were unable to work, as opposed to those being able to work, had 0.13 times lower odds of participating in vigorous PA (95% CI: 0.05, 0.38; p-value: <0.01) and of meeting the Canadian Movement Guidelines (95% CI: 0.05, 0.37; p-value: <0.01). Similarly, those that reported being unable to work spent on average 264.26 (95% CI: -414.42, -114.11; p-value: <0.01) minutes less doing moderate PA compared to those who did not report being unable to work, accounting for presence of postural orthostatic tachycardia and menstrual symptoms, gastrointestinal discomfort score, ability to work and IFAB score. Education was a significant predictor (p-value: 0.02) of weekly moderate PA; participants who reported completing university and college/CEGEP completed an average of 249.90 (95% CI: -274.87, 129.58; p-value: 0.02) and 72.64 (95% CI: -445.25, -54.56; p-value: 0.02) minutes less, respectively, than those who completed some or all of high school, accounting for the retained predictors.

Participants who reported using support aids either sometimes or always spent an average of 39.64 (95% CI: -66.75, -12.54; p-value: <0.01) minutes less performing muscle-strengthening activities, and had 0.49 (95% CI: 0.23, 1.02; p-value: 0.06) times the odds of participating in vigorous PA in a typical week compared to those that never used support aids when accounting for the respective model's predictors.

3.4 Discussion

Our study suggests that the characteristics, physical activity behaviors, and barriers and facilitators of PA between both diagnoses are similar. The study participants' medical and sociodemographic characteristics are consistent with those found in previous survey research.[16,36]

Our study described the duration of different PA types; it novelly demonstrated that muscle-strengthening PA as well as participation in vigorous-intensity PA and satisfaction of the Canadian Movement Guidelines recommendations are low in Canadians with hEDS/G-HSD. These are consistent with other findings of low PA in hEDS/G-HSD populations.[16,36] In the overall Canadian population, the PA recommendations were met in 49%, about 18% more than in people with hEDS/G-HSD.[37] Given that the most frequently performed moderate PAs by the study sample are activities of daily living, it could be stipulated that people with hEDS/G-HSD infrequently partake in scheduled exercise. This could contribute to the poor adherence to the Canadian Movement Guideline recommendations.

Our study was the first to quantitatively evaluate the individual and combined effects of various barriers and facilitators on PA levels in Canadians with hEDS/G-HSD. The IFAB score was positively associated with the duration of moderate and muscle-strengthening PA as well as the probability of participating in vigorous PA and meeting the Canadian Movement Guidelines.

Pain, gastrointestinal symptoms and fatigue were frequently reported by participants, with their median score signifying that these symptoms interrupt some activities or cause activity avoidance. The negative impact of these symptoms was solidified by the frequent listing of pain, fatigue and gastrointestinal issues as influential symptoms on PA. Despite participants frequently reporting a negative relationship between symptoms and PA participation, significant symptom variables in the regression analyses – presence of severe menstrual cramps or postural orthostatic tachycardia intolerance, and gastrointestinal discomfort rating – suggest that these symptoms increase duration of PA. This finding could be rationalized by the common use of PA as a treatment for these symptoms.[38–40] It has been suggested that PA in a horizontal position can improve postural

orthostatic tachycardia tolerance without triggering symptoms.[39] Likewise, research has found that gastrointestinal issues as well as menstrual symptoms can be mitigated by regular physical activity.[38,40] Hence, the contradiction in our results could indicate that people with hEDS/G-HSD experiencing these symptoms use PA as a treatment.

As evident by the median TSK-4 score of 11, there is a strong degree of kinesiophobia, which aligns with the median score of -6 for "a belief that PA makes symptoms worse" in the IFAB questionnaire. Kinesiophobia is very prevalent in studies of hEDS/G-HSD, as well as other chronic pain conditions, and has been shown to negatively impact PA participation.[16,41,42] Despite this, it was not shown to influence PA participation in the regression analyses, potentially due to its reduced importance when controlling for other predictors.

Given the uniqueness and complexity of hEDS and G-HSD, interventions aimed at increasing PA levels should be hEDS/G-HSD-targeted; however, no study of this kind has been done yet. PA education is a method that has been frequently used to promote PA behaviours in other conditions as it has the ability to provide and correct knowledge on PA, and encourage uptake.[43–45] Beyond this, adapting PA recommendations to the capabilities of individuals can promote adherence as this may reduce the burdensome effects of symptoms.[43,45] A program that 1. provides education on the hEDS/G-HSD-specific and general benefits of PA and how to exercise safely, and 2. is adapted to individual and population capabilities, may be a suitable intervention to mitigate barriers, notably kinesiophobia, symptoms' effects and a lack of knowledge, promote exercise confidence and increase PA levels.

This research is not without limitations. Given the nature of a survey and the need for participants to self-report an hEDS or G-HSD diagnosis, our results are subject to recall bias. Furthermore, this study is affected by selection bias from the recruitment methods – support groups, patient organizations and a rehabilitation clinic – as those who utilize these resources may have a more severe condition. Hence, the characteristics between the participants and those who chose not to participate may be different (i.e., condition severity, access to resources, knowledge on condition).

Our survey included reliable and valid questionnaires, but their metrics were not assessed specifically in hEDS/G-HSD populations. Additionally, the questionnaire was only tested by a single participant with hEDS and could have benefitted from more criticism. Also, our survey did not explicitly state to exclude muscle-strengthening PA from moderate or vigorous PA; therefore, the duration of the muscle-strengthening PA may be counted twice and increase the reported PA durations. Also, while the question on participants' moderate PA duration explicitly stated to exclude walking, this was not the case for the question on vigorous PA duration as walking is not traditionally a vigorous PA. Nevertheless, participants still listed walking in both vigorous and moderate PA. Due to these discrepancies, it was established that those who included the total number of days, daily walking time and listed walking in either moderate or vigorous PA would have their walking time subtracted from these two PA categories. Nonetheless, walking time may be included in the duration of moderate or vigorous PAs if these conditions were not met.

Non-response was present in half the variables used in the regression analysis, which accounted for 1.5% of the data; median imputation was used to deal with missing values for the regression analysis. The primary issue of this imputation strategy is biasing effect estimates towards the null, which may conceal some associations and affect our regression outputs. Given the low participation in PA and overwhelming presence of barriers, future studies should aim to develop, implement and evaluate interventions that mitigate barriers and promote PA in people with hEDS/G-HSD.

3.5 Conclusion

This study assessed the PA levels as well as the barriers and facilitators to PA in people with hEDS and G-HSD. Overall, the study found that the sample's PA participation was low with just over a third meeting the Canadian Movement Guidelines. This could be partially caused by the overwhelming presence and severity of symptoms as well as the prevalent belief that PA will make symptoms worse. The IFAB score was positively associated with all PA types and the probability to meet the Canadian Movement Guidelines. Future studies should investigate the effect of

addressing these barriers to increase PA participation given its important role in disorder management.

3.6 Supplementary Material

Supplementary Materials 1: Questionnaires

Validity and Reliability of Survey Questionnaires

Defense and Veterans Pain Rating Scale (DVPS)[20]

The DVPS showed a statistically significant moderate-high concurrent validity with other valid and reliable pain-related questionnaires, of which the Pain Disability Questionnaire (0.71) and the bodily pain subscale of the Veterans RAID 36-item Health Survey (-0.60) in DC Veteran Affairs Medical Center outpatients.[20] Likewise, another study in active duty service members and veterans showed acceptable internal reliability, with a Cronbach's alpha of 0.87, and test-retest reliability demonstrating correlations between 0.64 and 0.77.[46]

Tampa Kinesiophobia Scale 4-item[21]

The Tampa Kinesiophobia Scale 4-item (TKS-4) contains 4 components (item 3, 6, 7 and 11) of the original 13-item Tampa Kinesiophobia Scale.[21] TKS-4 was strongly correlated with the TKS (r = 0.86) and the Pain Catastrophizing Scale-4 item (r = 0.70).[21] It also demonstrated high internal consistency in musculoskeletal care patients; the authors concluded that the TKS-4 to be a good measure of kinesiophobia.[21]

Numeric Rating Scale[22]

A systematic review assessed the reliability and validity in the Numeric Rating Scale (NRS) determined that the NRS has a strong and good correlations to both the visual analogue scale and the VRS/VDS, respectively.[22] It also concluded that it is a reliable measure for pain and it is suitable for use.[22]

International Physical Activity Questionnaire – Short Form[31]

In a systematic review of the validity and reliability of the full-length International Physical Activity Questionnaire, the International Physical Activity Questionnaire - Short Form (IPAQ-SF)[31] demonstrated fair criterion validity in population samples originating from various countries including the United States, United Kingdom, Japan and Brazil.[31] The Spearman's coefficient was

0.30 between the IPAQ-SF and accelerometer data.[31] The reported coefficients for reliability and repeatability were 0.84 and 0.88, respectively, in the United States.[31]

Inflammatory Arthritis Facilitators and Barriers Questionnaire[32]

The Inflammatory Arthritis Facilitators and Barriers (IFAB) questionnaire has good convergent validity in individuals with rheumatoid arthritis, axial spondyloarthritis and/or psoriatic arthritis, with a significant correlation between the IFAB total score and the modified health assessment questionnaire of -0.24.[32] The authors also demonstrated that the questionnaire has good internal consistency with a Cronbach α values of 0.69.[32] However, it has never been used in people with hEDS/G-HSD.

Figure S3.1 Physical Activity Behaviours, Barriers and Facilitator's in People with Hypermobile Ehlers-Danlos Syndrome and Generalized Hypermobility Spectrum Disorder Questionnaire

Physical activity behaviors, barriers and facilitators in hypermobile Ehlers-Danlos and generalized hypermobility spectrum disorder

PARTICIPANT CONSENT FORM

Title of the study: Physical activity behaviors, barriers and facilitators in hypermobile Ehlers-Danlos syndrome and generalized hypermobility spectrum disorder: a survey

Principal Investigators: Annecy Houston, MSc. Student (anhousto@ualberta.ca; 780-248-1857) and Dr. Yan Yuan, PhD. (yyuan@ualberta.ca; 780-248-5853).

University of Alberta Ethics ID: PRO00124933

Version Date: January 5th, 2023

Invitation to Participate: You are being asked to participate in this survey about physical activity. This is because you are an adult diagnosed with hypermobile Ehlers-Danlos syndrome (hEDS) or generalized joint hypermobility spectrum disorder (G-HSD).

Purpose of the Study: This study aims to understand the physical activity habits of people with these conditions. It will also identify the factors that encourage and discourage people with your condition to participate in physical activities. This survey will be active until we have 150 to 200 submitted surveys.

Participation: If you wish to participate in this study, please complete the survey. The survey should take you about 15 to 20 minutes to complete. You do not have to answer any questions that you do not want to answer. When you finish the survey, please click the "submit" button.

Benefits: There are no benefits to you from completing the survey. This information can help plan strategies to promote physical activity in people with hypermobile conditions.

Risks: There are no severe risks from participation in the study, however participants may feel emotional distress when recalling a flare-up. If you require emotional support, resources for are provided at the end of the survey.

Confidentiality and Anonymity: The information that you will share will be confidential and only be used for this research. Only research team members will have access to your survey answers. Your answers to open-ended questions may be used as written in presentations and publications, but you will not be identified. Your answers will be combined with those of others. You are not being asked to provide your name or any personal information. Your participation will be anonymous.

Data Storage: Electronic copies of the survey will be protected with a password and stored securely on the University of Alberta server for a minimum of 5 years.

Compensation (or Reimbursement): There is no compensation for this study.

Voluntary Participation: You do not need to participate. If you choose to participate, you may refuse to answer questions that you do not want to answer. If you change your mind and do not want to participate at anytime during the survey, simply close the link and no responses will be included. If you choose to stop, but still want your answers included in the study, you may save your answers and quit. If you want to stop and continue the survey later, you may save your answers and quit. The survey is anonymous so when you submit your answers, it will no longer be possible to withdraw them from the study.

Information about the Study Results: If you want to get the study results once the study is done, please email Annecy Houston (anhousto@ualberta.ca).

Contact Information: If you have any questions, want more information about the study, or require help to complete the survey, you may contact Annecy Houston (anhousto@ualberta.ca; 780-248-1857).

The plan for this study has been approved by the Research Ethics Board at the University of Alberta. If you have any questions about your rights as a participant or how the study is being conducted, you may contact the Research Ethics Office at 780-492-2615.

Please print or save a copy of this form for your records.

Saving or submitting the survey means you consent to participate.

Section 1: Medical Questions	
Do you have a diagnosis of hypermobile Ehlers-Danlos Syndrome (hEDS) or Generalized Hypermobility Spectrum Disorder (G-HSD)?	◯ Yes; hEDS ◯ Yes; G-HSD ◯ hEDS or G-HSD is suspected ◯ No
What type of healthcare provider diagnosed you?	◯ Geneticist ◯ Rheumatologist ◯ Family Physician ◯ Pediatrician ◯ Other
Please specify "Other":	_____
Which of the following conditions/symptoms do you experience?	☐ Pain ☐ Dislocations ☐ Subluxations ☐ Fatigue ☐ Gastrointestinal discomforts ☐ Severe menstrual cramps ☐ Headaches ☐ Migraines ☐ Anxiety and/or depression ☐ A neurodivergent condition (e.g. ADHD, dyslexia,...) ☐ Panic disorder ☐ Postural orthostatic tachycardia intolerance ☐ Pelvic floor/bladder dysfunction ☐ Mast cell activation syndrome

What is your year of birth?

- ◯ 2005
- ◯ 2004
- ◯ 2003
- ◯ 2002
- ◯ 2001
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	◯ 1936 ◯ 1935 ◯ 1934 ◯ 1933 ◯ 1932 ◯ 1931 ◯ 1930 ◯ 1929 ◯ 1928 ◯ 1927 ◯ 1926 ◯ 1925 ◯ 1924 ◯ 1923 ◯ 1922 ◯ 1921 ◯ 1920 ◯ 1919 ◯ 1918 ◯ 1917 ◯ 1916 ◯ 1915 ◯ 1914 ◯ 1913 ◯ 1912 ◯ 1911 ◯ 1910
At what life stage did you start having symptoms associated with hypermobile Ehlers-Danlos Syndrome (hEDS) or Generalized Hypermobility Spectrum Disorder (G-HSD)?	◯ Infancy (birth-2 years old) ◯ Childhood (3-12 years old) ◯ Adolescence (13-19 years old) ◯ 20-29 years old ◯ 30-39 years old ◯ 40 years old and more
What intensity would you rate your pain on average? Please refer to the scale on the following image. [Attachment: "Pain Scale.png"]	
	0 5 10 *(Place a mark on the scale above)*
During a typical 7-day period, how severe are your gastrointestinal symptoms on average?	0 5 10 *(Place a mark on the scale above)*
During a typical 7-day period, how severe is your fatigue on average?	0 5 10 *(Place a mark on the scale above)*
For the following questions, please rate the statements on a scale of "strongly disagree" to "strongly agree."	
My body is telling me I have something dangerously wrong.	◯ Strongly disagree ◯ Somewhat disagree ◯ Somewhat agree ◯ Strongly agree

hEDS or G-HSD has put my body at risk for the rest of my life.	○ Strongly disagree ○ Somewhat disagree ○ Somewhat agree ○ Strongly agree
Pain always means I have injured my body.	○ Strongly disagree ○ Somewhat disagree ○ Somewhat agree ○ Strongly agree
I wouldn't have this much pain if there weren't something potentially dangerous going on in my body.	○ Strongly disagree ○ Somewhat disagree ○ Somewhat agree ○ Strongly agree
Are you currently in a flare-up period or a temporary period where your physical activity levels are altered (e.g., healing from a surgery, injury...)? A flare-up period is defined as a period of higher-than-normal condition severity .	○ Yes ○ No
How severe is your flare-up?	Mild flare-up Moderate flare-up Severe flare-up *(Place a mark on the scale above)*
When did your flare-up start?	_____
Please describe your flare-up/circumstances by including the affected area(s), the suspected cause(s) and any other information that you may think is pertinent.	_____
Do you use mobility aids such as a wheelchair, walker, scooter, walking poles, crutches or cane?	○ Always ○ Sometimes ○ Never
What mobility aids do you use?	☐ Manuel wheelchair ☐ Electric wheelchair ☐ Standing wheelchair ☐ Scooter ☐ Braces ☐ Walker ☐ Cane ☐ Crutches ☐ Walking poles ☐ Other
Please specify "Other":	_____
Why do you use the selected mobility aids (e.g., pain, balance, dizziness...)?	_____

Section 2: Sociodemographic Questions

The following questions are only used to describe our participants. Your answers will be grouped with the answers of other participants.

Which province do you reside in?	◯ Ontario ◯ British Columbia ◯ Alberta ◯ Quebec ◯ Saskatchewan ◯ Manitoba ◯ Prince Edward Island ◯ New Brunswick ◯ Newfoundland and Labrador ◯ Nova Scotia ◯ Yukon ◯ Northwest Territories ◯ Nunavut
What were the ethnic or cultural origins of your ancestors? (Choose all that apply)	☐ North American ☐ African ☐ European ☐ Asian ☐ Southeast Asian ☐ Oceanian ☐ Central and South American ☐ Other ☐ Prefer not to answer
Please specify "Other":	_____
With which gender do you most identify?	◯ Woman ◯ Man ◯ Transgender woman ◯ Transgender man ◯ Non-binary ◯ Two-Spirit ◯ Other ◯ Prefer not to answer
Please specify "Other" if selected:	_____
What is your marital status?	◯ Single ◯ Married, or in a domestic partnership (common law) ◯ Widowed ◯ Separated or divorced
What is the highest degree or level of school you have completed?	◯ Less than a high school degree ◯ High school degree ◯ College/CEGEP ◯ University or higher ◯ Other
Please specify "Other":	_____

What is your current employment status? (Choose all that apply)	☐ Full-time (30 or more hours per week) ☐ Part-time (up to 29 hours per week) ☐ Unemployed ☐ Student ☐ Retired ☐ Homemaker ☐ Self-employed ☐ Unable to work ☐ Other
Please specify "Other" if selected:	_____
What is your best estimate of your personal income last year (includes employment, pension, social benefits and investments) before deductions?	◯ Less than $9,999 ◯ $10,000-$24,999 ◯ $25,000-$49,999 ◯ $50,000-$74,999 ◯ $75,000-$99,999 ◯ $100,000-$149,999 ◯ More than $150,000 ◯ Prefer not to answer
What is your best estimate of your household income last year (includes employment, pension, social benefits and investments) before deductions?	◯ Less than $9,999 ◯ $10,000-$24,999 ◯ $25,000-$49,999 ◯ $50,000-$74,999 ◯ $75,000-$99,999 ◯ $100,000-$149,999 ◯ More than $150,000 ◯ Prefer not to answer

Section 3: Physical Activity Behaviors

Think about all the vigorous activities that you do in a typical 7-day period, irrespective of flare-ups. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal (between 77% and 93% of your max heart rate). Think only about those physical activities that you do for at least 10 minutes at a time.

1. During a typical 7-day period, on how many days do you do vigorous physical activities like heavy lifting, digging, aerobics or fast bicycling?	◯ No vigorous physical activity ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7
How much time do you usually spend doing vigorous physical activities on one of those days?	
Hours per day:	_____
Minutes per day:	_____
Please list up to 3 vigorous physical activities you do the most:	_____

Think about all the moderate activities that you do in a typical 7-day period, irrespective of flare-ups. Moderate physical activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal (between 64% and 76% of your max heart rate). Think only about those physical activities that you do for at least 10 minutes at a time.

2. During a typical 7-day period, on how many days do you do moderate physical activities like carrying light loads, bicycling at a regular pace or scrubbing floors? Do not include walking.

- ◯ No moderate physical activity
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7

How much time do you usually spend doing moderate physical activities on one of those days?

Hours per day: _____

Minutes per day: _____

Please list up to 3 moderate physical activities you do the most: _____

Think about all the muscle-strengthening activities that you do in a typical 7-day period, irrespective of flare-ups. Muscle-strengthening activities refer to activities that are done to build muscle and strength.

3. During a typical 7-day period, on how many days do you do muscle-strengthening activities like body-weight exercises, using resistance bands or lifting weights?

- ◯ No muscle-strengthening activities
- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7

How much time do you usually spend doing muscle-strengthening activities on one of those days?

Hours per day: _____

Minutes per day: _____

Please list up to 3 muscle-strengthening activities you do the most: _____

Think about the time you spend walking in a typical 7-day period, irrespective of flare-ups. This includes at work and at home, walking to travel from place to place, and any other walking that you do solely for recreation, sport, exercise, or leisure.

4. During a typical 7-day period, on how many days do you walk for at least 10 minutes at a time?

- ◯ No walking
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7

How much time do you usually spend walking on one of those days?

Hours per day: _____

Minutes per day: _____

The last questions are about the time you spend sitting/lying and stretching during a typical 7-day period, irrespective of flare-ups. Sitting/lying includes time spent at work and at home during waking hours. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

6. During a typical 7-day period, how much time do you spend stretching and/or foam rolling?

Hours per day: _____

Minutes per day: _____

5. During a typical 7-day period, how much time do you spend sitting/lying down?

Hours per day: _____

Minutes per day: _____

SECTION 4: FACILITATORS AND BARRIERS TO PHYSICAL ACTIVITY

Please take few moments to think about all the physical activity you did in the previous month: walking, jogging, gardening and other kind of sports. Now, think about all the things that have encouraged you, and all the things that prevented you from doing physical activity in the previous month. The following questions aim to collect information on all the things that have encouraged you or prevented you from doing physical activity in the previous month.

Please indicate for each item if it has rather encouraged you, prevented you, or had no impact on your physical activity in the previous month (only one answer) and rate the importance.

A: Items that may have encouraged me or prevented me from doing physical activity in the last month.

1. Level of symptoms (pain, fatigue, instability, dizziness, GI issues...)	○ rather prevented me from doing physical activity in the previous month ○ rather encouraged me to do physical activity in the previous month
Rate the importance of the impact:	Had no impact on my physical activity — Had maximal impact on my physical activity *(Place a mark on the scale above)*
What symptoms encouraged/prevented you the most from doing physical activity in the last month? List up to three:	_____
2. Weather conditions	○ rather prevented me from doing physical activity in the previous month ○ rather encouraged me to do physical activity in the previous month
Rate the importance of the impact:	Had no impact on my physical activity — Had maximal impact on my physical activity *(Place a mark on the scale above)*
3. Support from others (friends, family)	○ rather prevented me from doing physical activity in the previous month ○ rather encouraged me to do physical activity in the previous month
Rate the importance of the impact:	Had no impact on my physical activity — Had maximal impact on my physical activity *(Place a mark on the scale above)*
4. Support and/or advice from healthcare professionals	○ rather prevented me from doing physical activity in the previous month ○ rather encouraged me to do physical activity in the previous month
Rate the importance of the impact:	Had no impact on my physical activity — Had maximal impact on my physical activity *(Place a mark on the scale above)*
5. Access to activity facilities (e.g., area for walking, gym...) and/or supportive equipment (e.g., KT tape, braces,...)	○ rather prevented me from doing physical activity in the previous month ○ rather encouraged me to do physical activity in the previous month
Rate the importance of the impact:	Had no impact on my physical activity — Had maximal impact on my physical activity *(Place a mark on the scale above)*

B: Items that may have prevented me from doing physical activity in the last month.

6. A belief that physical activity will make my symptoms worse

Rate the importance of the impact:

Had no impact on my physical activity — Had maximal impact on my physical activity

(Place a mark on the scale above)

7. Lack of motivation

Rate the importance of the impact:

Had no impact on my physical activity — Had maximal impact on my physical activity

(Place a mark on the scale above)

8. Lack of time

Rate the importance of the impact:

Had no impact on my physical activity — Had maximal impact on my physical activity

(Place a mark on the scale above)

9. Lack of knowledge on which exercises to do, how much and how often

Rate the importance of the impact:

Had no impact on my physical activity — Had maximal impact on my physical activity

(Place a mark on the scale above)

10. Lack of knowledge of benefits of physical activity for general health and/or condition management

Rate the importance of the impact:

Had no impact on my physical activity — Had maximal impact on my physical activity

(Place a mark on the scale above)

11. Lack of knowledge of benefits of physical activity for mood

Rate the importance of the impact:

Had no impact on my physical activity — Had maximal impact on my physical activity

(Place a mark on the scale above)

12. Limited confidence on how to exercise safely

Rate the importance of the impact:

Had no impact on my physical activity — Had maximal impact on my physical activity

(Place a mark on the scale above)

13. Are there any other factors that prevent or encourage your participation in physical activity? Please list and describe them in the following text box.

Thank you for participating in the study. If you would like to be informed of the results of our study once completed, please email anhousto@ualberta.ca.

If you desire emotional support after answering this survey, please contact get in contact with a Wellness Together Canada counsellor by phone at 1-866-585-0445, or visit Wellness Together Canada's website https://www.wellnesstogether.ca/en-CA?lang=en-ca for mental health support options.

Supplementary Materials 2: Candidate Predictor Variables

Table S3.1 Candidate Predictor Variables

Variables	
Total barrier and facilitator score	Diagnosis group
-120 to 50	hEDS
	G-HSD
Age	Age at start of symptom appearance
18-29 years old	0-2 years old
30-39 years old	3-12 years old
40-49 years old	13-19 years old
50-59 years old	20-29 years old
60+ years old	30+ years old
Marital status	Highest level of education completed
Single	Less than a high school /high school
Married/domestic partnership	College/CEGEP
Widowed/separated/divorced	University or higher
Gender	Presence of a flare-up
Woman	Yes
Other	No
Kinesiophobia score	Pain rating
4 to 16	0 to 10
Gastrointestinal discomfort rating	Fatigue rating
0 to 10	0 to 10
Use of support aids	Work
Never	Full-time
Sometimes/always	Unemployed
Unable to work	Presence of dislocations
Yes	Yes
No	No
Presence of subluxations	Presence of postural orthostatic tachycardia intolerance
Yes	Yes
No	No
Presence of anxiety or depression	Presence of pelvic issues/bladder dysfunction
Yes	Yes
No	No
Presence of headaches or migraines	Presence of mast cell activation syndrome
Yes	Yes
No	No
Presence of severe menstrual symptoms	Presence of a panic disorder
Yes	Yes
No	No
Presence of a neurodivergent condition	Total number of the listed conditions/symptoms
Yes	0 to 14
No	
North American	African
Yes	Yes
No	No
European	Asian
Yes	Yes
No	No

Aboriginal
Yes
No

Supplementary Materials 3: Sociodemographic and Medical Characteristics, and Physical Activity Behaviours, Barriers and Facilitators by Diagnosis Group

Table S3.2 Sociodemographic Characteristics

		hEDS (n = 143; 77.3%)	G-HSD (n = 42; 22.7%)	p-value
Age				0.34
	Median (IQR)	42 (17)	41 (17)	
	Missing (n [%])	4 (2.2)	1 (2.4)	
Gender (n [%])				0.39
	Woman	129 (90.2)	34 (81.0)	
	Non-binary	11 (7.7)	6 (14.3)	
	Man	3 (2.1)	1 (2.4)	
	Missing	0 (0.0)	1 (2.4)	
Ethnicity (n [%])[a]				
	European	108 (75.5)	38 (90.5)	0.04
	North American	53 (37.1)	12 (28.6)	0.31
	Aboriginal	6 (4.2)	2 (4.8)	0.87
	Asian	7 (4.9)	0 (0.0)	0.14
	African	6 (4.2)	0 (0.0)	0.18
	Central-South American	2 (1.4)	0 (0.0)	0.44
	South-Est Asian	1 (0.7)	1 (2.4)	0.35
	Missing	6 (4.2)	0 (0.0)	0.12
Province of residence (n [%])				0.09
	Ontario	49 (34.3)	23 (54.8)	
	British Columbia	32 (22.4)	7 (16.7)	
	Prairies	31 (21.7)	6 (14.3)	
	Quebec	11 (7.7)	6 (14.3)	
	Maritimes/Newfoundland and Labrador	11 (7.7)	0 (0.0)	
	Yukon	1 (0.7)	0 (0.0)	
	Missing	8 (5.6)	0 (0.0)	
Education (n [%])				0.85
	University or higher degree	61 (42.7)	16 (38.1)	
	College/CEGEP degree	44 (30.8)	14 (33.3)	
	High school degree	26 (18.2)	7 (16.7)	
	Less than a high school degree	2 (1.4)	0 (0)	
	Missing	10 (7.0)	5 (11.9)	
Work status (n [%])[a]				
	Unable to work	53 (37.1)	8 (19.1)	0.03
	Full-time	37 (25.9)	14 (33.3)	0.34
	Part-time	25 (17.5)	8 (19.1)	0.82
	Self-employed	18 (12.6)	5 (11.9)	0.91
	Student	14 (9.8)	7 (16.7)	0.22
	Unemployed	11 (7.7)	4 (9.5)	0.70
	Homemaker	8 (5.6)	2 (4.8)	0.83
	Retired	8 (5.6)	0 (0.0)	0.12
	Missing	0 (0.0)	0 (0.0)	-

[a] participants could check multiple options.

Table S3.3 Medical Characteristics

	hEDS (n = 143; 77.3%)	G-HSD (n = 42; 22.7%)	p-value
Start period (n [%])			0.36
Childhood	76 (53.2)	24 (57.1)	
Adolescent	26 (18.2)	9 (21.4)	
Infancy	19 (13.3)	4 (9.5)	
20-29 years old	9 (6.3)	4 (9.5)	
30 years and more	11 (7.7)	0 (0.0)	
Missing	2 (1.4)	1 (2.4)	
Diagnosis provider (n [%])			<0.01
Geneticist	75 (52.5)	5 (11.9)	
Rheumatologist	26 (18.2)	13 (31.0)	
Family physician/pediatrician/internist	23 (16.1)	8 (19.1)	
Physiatrist/orthopedist/pain specialist	12 (8.4)	16 (38.1)	
Other	5 (3.5)	0 (0.0)	
Missing	2 (1.4)	0 (0.0)	
Symptom occurrence (n [%])[a]			
Pain	142 (99.3)	41 (97.6)	0.35
Fatigue	134 (93.7)	39 (92.9)	0.84
Subluxations/dislocations	133 (93.0)	39 (92.9)	0.97
Gastrointestinal dysfunction	125 (87.4)	37 (88.1)	0.91
Headaches/migraines	112 (78.3)	30 (71.4)	0.35
Anxiety, depression or panic disorder	107 (74.8)	30 (71.4)	0.66
Postural orthostatic tachycardia intolerance	85 (59.4)	16 (38.1)	0.02
Pelvic floor and/or bladder dysfunction	78 (54.6)	21 (50.0)	0.60
Severe menstrual cramps[b]	71 (55.0)	16 (47.1)	0.19
Neurodivergent condition	74 (51.8)	18 (42.9)	0.31
Mast cell activation syndrome	70 (49.0)	13 (31.0)	0.04
Missing	0 (0.0)	0 (0.0)	-
Defense and Veterans Pain Rating Scale[c]			0.12
Median (IQR)	6 (2)	5 (2)	
Missing (n [%])	5 (3.5)	2 (4.8)	
Gastrointestinal discomfort on the Numeric Rating Scale[c]			0.34
Median (IQR)	4 (3)	5 (4)	
Missing (n [%])	5 (3.5)	0 (0.0)	
Fatigue on the Numeric Rating Scale[c]			0.04
Median (IQR)	7 (2)	6.5 (2)	
Missing (n [%])	1 (0.7)	0 (0.0)	
Kinesiophobia score[d]			0.78
Median (IQR)	11 (4)	11 (3)	
Missing (n [%])	3 (2.1)	2 (4.8)	

[a] participants could check multiple options; [b] out of 129 women with hEDS and 34 women with G-HSD; [c] ranges from 0 to 10; [d] measured by the Tampa Scale for Kinesiophobia Short Form which ranges from 4 to 14.

Table S3.4 Physical Activity Types, Frequency and Duration

Types of PA (median [IQR])	hEDS (n = 143)	G-HSD (n = 42)	p-value
Vigorous PA			
n (%)	45 (31.5)	18 (42.9)	0.48
Days per week	0 (1)	0 (2)	0.25
Minutes per week	0 (60)	0 (90)	0.18
Moderate PA			
n (%)	107 (74.8)	30 (71.4)	0.74
Days per week	2 (4)	2.5 (5)	0.94
Minutes per week	120 (300)	87.5 (240)	0.62
Muscle-strengthening PA			
n (%)	73 (51.0)	24 (57.1)	0.07
Days per week	1 (3)	1 (3)	0.77
Minutes per week	15 (120)	37.5 (120)	0.24
Meeting the Canadian Movement Guidelines			
n (%)	49 (34.3)	10 (23.8)	0.20

Table 65 Barriers and Facilitators to Physical Activity

	Median (IQR)		
	hEDS (n = 143)	G-HSD (n = 42)	p-value
Barriers or facilitators (-10 to 10)			
Symptoms	-8 (3)	-7 (3)	0.10
Weather	-6 (5)	-5 (6.5)	0.10
Support from friends and family	5 (5)	6 (6)	0.22
Support from healthcare professionals	3 (6)	5 (6)	0.36
Access to facilities	3 (12)	5 (11)	0.42
Barriers (-10 to 0)			
A belief that PA makes symptoms worse	-6 (6)	-6 (6)	0.83
Lack of motivation	-5 (5)	-5 (4)	0.87
Lack of time	-3 (6)	-4 (6)	0.82
Lack of knowledge on which exercises to do, how much and how often	-3 (6)	-3 (7)	0.89
Lack of knowledge of benefits of physical activity for general health and/or condition management	-1 (3)	-1 (2)	0.96
Lack of knowledge of benefits of physical activity for mood	-1 (3)	-0.5 (2)	0.84
Limited confidence on how to exercise safely	-4 (6)	-6 (7)	0.19
Total IFAB score	-29.5 (30.5)	-26.5 (24)	0.56

Supplementary Materials 4: Qualitative Analysis Results of Open-ended Questions.
Table S3.6 Reasons for Mobility Aid Use

Reasons	Prevalence (n = 89; 47.9%)
Pain	57
Imbalance	44
Joint instability	26
Dizziness	20
Muscle fatigue	13
Dislocation/subluxation	11
Dysautonomia	11
Fatigue	10
Injury or irritation of injury	6
Proprioception deficits	4
To carry items	2
Reduce joint stress	2
Loss of function	2
Management of an injury	2
Blood circulation	1
Numbness in legs	1
Spasms	1
Nausea	1
Medical alert	1

Table S3.7 Flare-Up Symptoms

Symptoms	Sample (n = 98; 52.7%)
Musculoskeletal pain	55
Subluxations/dislocations	20
Headache/migraine	16
Fatigue	15
Gastrointestinal irritation	13
Dysautonomia	9
Mast cell activation syndrome flare	6
Mobility restrictions	6
Difficulty eating	5
Spasms	5
Loose joints	4
Vertigo	2
Constantly cold	2
Circulatory issues	2
Eye issues	2
Muscle strain	2
Anxiety/depression	2
Disordered sleep	2
Soreness	2
Difficulty breathing	2
Urinary dysfunctions	2
Malaise	1
Coordination	1
Iron deficiency	1
Brain fog	1
Sensory hypersensitivity	1
Flu-like symptoms	1
Necrosis	1

Table S3.8 Reported Flare-Up Causes

Causes	Prevalence (n = 98; 52.7%)
Injury	11
Stress	9
Subluxation/dislocation	9
Weather	9
Work	7
Overexertion	7
Menstrual cycle	7
Unknown	6
Viral infection	5
New medication	3
Surgery	3
Lack of exercise	3
Exercise	3
Rheumatological disorder	3
Pregnancy	2
Car accident	2
Anaphylaxis	2
Food	2
Mental illness	2
Wrapping present on floor	1
GI issue	1
Uterine fibroid	1
Bad shoes	1
Loose joints	1
Mental unwellness	1
C-section	1
Air travel	1
Moving homes	1
Driving	1
Caught someone falling off wheelchair	1
Drug use	1

Table S3.9 Vigorous Physical Activities

Vigorous Physical Activities	Prevalence (n = 63; 34.4%)
Walking	24
Weightlifting	17
Cycling (indoor or outdoor)	15
Swimming	9
Dancing	7
Running	7
Aerobics	7
Skiing	5
Circuit training/High intensity interval training	4
Jogging	4
Elliptical	4
Stair-climbing and -descending	4
Rowing	4
House and yard work	4
Carrying heavy loads	4
Strength training	3
Bodyweight exercises	3
Pilates	3
Martial arts	2
Jumping	2
Pulling/pushing	2
Curling	1
Ping pong	1
Hula hooping	1
Soccer	1
Horseback ridding	1
Standing	1

Table S3.10 Moderate Physical Activities

Moderate Physical Activities	Prevalence (n = 137; 74.5%)
House and yard work	90
Walking	46
Carrying loads	39
Stair-climbing and -descending	16
Cycling (indoor or outdoor)	14
Physiotherapy exercises	10
Swimming/aquafit	9
Playing with dog/kids	8
Errands/appointments	8
Pilates	7
Jogging	6
Work	5
Skiing	4
Light exercise (unspecified)	4
Yoga	4
Dancing	3
Activities of daily living	3
Weightlifting	3
Elliptical	2
Hula hooping	2
Pulling/pushing	2
Curling	1
Vibration plate	1
Skating	1
Running	1
Roller blading	1
Aerobics	1
Body-weight exercises	1
Tai Chi	1
Horseback ridding	1
Rowing	1
Massage therapy	1
Exercise videos	1

Table S3.11 Muscle-Strengthening Physical Activities

Muscle-Strengthening Activities	Prevalence (n = 91; 51.9%)
Lifting weights	39
Resistance bands/cables	35
Bodyweight exercises	34
Physiotherapy exercises	26
Pilates	12
Yoga	8
Targeted exercises	5
Aqua therapy/swimming	3
Walking	3
Fitness class (unspecified)	2
Weight machines	1
High intensity interval training	1
Isometric exercises	1
Balance exercises	1
Martial arts	1
Dance	1
Stretching	1
Grocery shopping	1
Lifting and carrying	1
Indoor cycling	1
Housework	1

Table S3.12 Influential Symptoms on Physical Activity

Influential Symptoms on PA	Frequency
Pain	133
Fatigue	85
Subluxation/dislocations	30
Dizziness/fainting	29
GI issues	22
Migraines/headaches	18
Fear of injury and/or pain	18
Dysautonomia	16
Nausea/vomiting	16
Soreness	9
Joint instability	8
Weakness	7
Injuries	6
Arthritis	5
Malaise	3
Shortness of breath	3
Mobility	3
Diarrhea	3
Anxiety/depression	3
Chest pain	2
Flu	2
Flare-up	2
Inflammation	2
Self-efficacy	2
Cardiovascular issues	2
Mental wellness	2
Hypersensitivities (sound, light, allergies)	2
Bladder/pelvic floor dysfunction	2
Menstrual pain	1
Cramping	1
Palpitations	1
Skin splitting	1
Balance	1
Throat swelling	1
Asthma and congestion	1
Numbness	1
Healing from surgery	1
Heartburn	1
Brain fog	1
Medication side effects	1
Other medical conditions	1

Table S3.13 Other Barriers and Facilitators to Physical Activity

Other barriers and facilitators	Frequency
Access to EDS-knowledgeable HCP	12
Cost	10
Cost of and regular access to HCP	6
Having a pet or an exercise buddy	4
Public health safety measures in recreational facilities	2
Having a routine	2
Embarrassment around peers	1
Lack of childcare	1
Progress in symptom severity	1
Post-exercise feeling	1
Passion for exercise	1

Supplementary Materials 5: Significant (p-value<0.20) Univariate Associations

Table S3.14 Significant Univariate Associations with Meeting the Canadian Movement Guidelines

	Odds ratio (95% CI)	p-value
Total IFAB score[a]	1.03 (1.01; 1.04)	<0.01
Education		0.19
University or higher 2	1.92 (0.85; 4.30)	
College/CEGEP	1.22 (0.51; 2.93)	
Highschool or less (ref[b])	—	
Unable to work		
Yes	0.45 (0.23; 0.86)	0.01
No (ref)	—	—
Pain numeric rating scale score[c]	0.79 (0.65; 0.97)	0.02
Kinesiophobia score[d]	0.79 (0.69; 0.90)	<0.01
Use of support aids		
Sometimes/always	0.55 (0.31; 0.99)	0.04
Never (ref)	—	—

[a] Inflammatory Arthritis Facilitators and Barriers, ranging from -120 to 50; [b] reference group; [c] ranges from 0 (none) to 10 (severest); [d] measured by the Tampa Scale for Kinesiophobia Short Form which ranges from 4 to 14.

Table S3.15 Significant (p-value<0.20) Univariate Associations with Participating in Vigorous Physical Activities in a Typical Week

	Odds ratio (95% CI)	p-value
Total IFAB score[a]	1.03 (1.01; 1.04)	<0.01
Education		0.08
University or higher 2	2.74 (1.08;6.93)	
College/CEGEP	2.21 (0.83; 5.92)	
Highschool or less (ref[b])	—	
Unable to work		
Yes	0.11 (0.04; 0.28)	<0.01
No (ref)	—	—
Gastrointestinal discomfort score[c]	0.86 (0.75; 0.99)	0.03
Pain score[c]	0.58 (0.46; 0.74)	<0.01
Fatigue score[c]	0.77 (0.65; 0.91)	<0.01
Work		
Full-time	0.29 (0.07; 1.16)	0.08
Unemployed (ref)	—	—
Kinesiophobia score[d]	0.81 (0.71; 0.92)	<0.01
Use of support aids		
Sometimes/always	0.33 (0.17; 0.62)	<0.01
Never (ref)	—	—
North American ethnicity		
Yes	1.70 (0.91; 3.17)	0.10
No (ref)	—	—

[a] Inflammatory Arthritis Facilitators and Barriers, ranging from -120 to 50; [b] reference group; [c] ranges from 0 (none) to 10 (severest); [d] measured by the Tampa Scale for Kinesiophobia Short Form which ranges from 4 to 14.

Table S3.16 Significant (p-value<0.20) Univariate Associations with Duration of Moderate Physical Activities per Week (Minutes)

	Coefficient (95% CI)	p-value
Education		0.2
University or higher	-50.41 (-222.54; 265.14)	
College/CEGEP	80.76 (-103.63; 265.14)	
Highschool or less (ref[a])	—	
Unable to work		
Yes	-200.21 (-333.76; -66.66)	<0.01
No (ref)	—	—
Work		
Full-time	-251.67 (-536.33; 32.98)	0.08
Unemployed (ref)	—	—
Gastrointestinal discomfort score[b]	23.70 (-3.61; 51.00)	0.09
Use of support aids		
Sometimes/always	-145.67 (-271.03; -20.30)	0.02
Never (ref)	—	—
Presence of postural orthostatic tachycardia syndrome		
Yes	106.88 (-19.57; 233.33)	0.10
No (ref)	—	—
North American ethnicity		
Yes	117.64 (-14.62; 249.89)	0.08
No (ref)	—	—

[a] reference group; [b] ranges from 0 (none) to 10 (severest).

Table S3.17 Significant (p-value<0.20) Univariate Associations with Duration of Muscle-Strengthening Physical Activities per Week (Minutes)

	Coefficient (95% CI)	p-value
Total IFAB score[a]	0.27 (0.12; 0.42)	<0.01
Age		<0.01
60+ years old	-22.05 (-35.65; -8.46)	
50-59 years old	-17.51 (-29.44; -5.57)	
40-49 years old	-7.61 (-16.65; 1.43)	
30-39 years old	-6.05 (-16.12; 4.02	
18-29 years old (ref[b])	—	
Unable to work		
Yes	-7.68 (-14.94; -0.42)	0.04
No (ref)	—	—
Pain score[c]	-2.98 (-5.27; -0.69)	0.01
Kinesiophobia score[d]	-1.07 (-2.40; 0.26)	0.11
Use of support aids		
Sometimes/always	-9.67 (-16.37; -2.97)	<0.01
Never (ref)	—	—
Presence of menstrual symptoms		
Yes	4.61 (-2.21; 11.42)	0.18
No (ref)	—	—
European ethnicity		
Yes	-5.73 (-13.96; 2.49)	0.17
No (ref)	—	—
Aboriginal ethnicity		
Yes	-12.06 (-28.66; 4.55)	0.15
No (ref)	—	—

[a] Inflammatory Arthritis Facilitators and Barriers, ranging from -120 to 50; [b] reference group; [c] ranges from 0 (none) to 10 (severest); [d] measured by the Tampa Scale for Kinesiophobia Short Form which ranges from 4 to 14.

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4.0 CHAPTER 4: Discussion

Hypermobile Ehlers-Danlos Syndrome and Generalized Hypermobility Spectrum Disorder (hEDS/G-HSD) are connective tissue disorders characterized by hypermobile joints and musculoskeletal consequences such as joint instability, subluxations, dislocations, injury and pain.[1] Manifestations extend to multisystemic symptoms such as fatigue, autonomic dysfunction, gastrointestinal and mast cell dysfunction, migraines and headaches.[1] Given the absence of a known cure for hEDS/G-HSD, symptom prevention and management is a major component for wellbeing when living with these disorders. Physical activity (PA) is deemed one of the most effective management strategies as it is thought to reduce many symptoms experienced by people with hEDS/G-HSD. [2–12]

This study set out to assess the effectiveness of PA on various hEDS/G-HSD symptoms through a literature review, as well as determine current participation in different types of PA and the barriers and facilitators that lead to their uptake using a survey. As a result, this work provides a complete overview, in terms of PA types, benefits and uptake potential based on external and internal factors, of PA as a symptom management tool in hEDS/G-HSD.

4.1 Summary of Findings

4.1.1 Benefits of PA

Given their predisposition to musculoskeletal symptoms, PA's advantages may be further beneficial in people with hEDS/G-HSD. Intervention trials in this population demonstrate that PA, specifically muscle-strengthening PAs, can reduce joint instability, as well as improve muscle strength and endurance. These benefits agree with results in other musculoskeletal disorders such as rheumatoid arthritis,[13] osteoarthritis,[14] fibromyalgia[15] and other chronic pain conditions.[15] In other populations, range of motion seems to increase with PA.[14,16] Interestingly, the current evidence in hEDS/G-HSD suggest a decrease or no effect on range of motion following high-resistance interventions.[10,11] Many hEDS/G-HSD symptoms are musculoskeletal (i.e., pain, subluxations/dislocations, injuries), therefore the increase in joint stability, and muscle strength and endurance from PA can positively affect these symptoms and improve overall functioning.

The PA programs trialed in hEDS/G-HSD also demonstrated improvements in pain, proprioception, balance, fatigue, kinesiophobia, functional capabilities and disability. [2–12] Similar positive effects of PA on these outcomes is seen in people with other musculoskeletal diseases.[13–15] Improvements in these domains may significantly increase quality of life and wellness in people with hEDS/G-HSD.[17–19]

4.1.2 Implementation of PA

This analysis demonstrated that PA participation is low and the Canadian Movement Guidelines are infrequently met in Canadians with hEDS/G-HSD, which aligns with other findings in hEDS/G-HSD[20] and other musculoskeletal disorders.[21,22] However, it is now understood that people with hEDS/G-HSD scarcely partake in scheduled and planned PA, notably in vigorous and muscle-strengthening PAs. This is unfortunate given the potential of muscle-strengthening PAs for symptom management. The presence of barriers were overwhelming; the most prominent barrier to PA was symptoms – notably pain, fatigue, subluxations/dislocations. These symptoms have also been shown to improve with participation in PA. [2,3,5,6,8–12] Also, as demonstrated in Chapter 3, it is now known that PA participation predictors can vary according to the type of PA, which should be considered when encouraging PA-specific engagement.

Participants did not report a lack of knowledge on the benefits of PA for symptom management and mood on average, but did report limited confidence on exercising safely and a paucity in knowledge on exercise execution. We can therefore stipulate that there is a disconnect between PA recommendations and application. This gap could be filled by investigating the outcomes of providing a partly supervised PA program for people with hEDS/G-HSD's capabilities and ensuring confidence with movements prior to individual application. This, coupled with gradual exercise progressions, may increase PA levels without triggering a flare-up while simultaneously improving symptom severity. Furthermore, kinesiophobia was very prevalent and severe among individuals with hEDS/G-HSD, which was foreseen given its high prevalence in people with other musculoskeletal disorders.[23,24] Trials aiming to reduce this fear in in people with non-specific low-

back[25] and neck pain,[26] fibromyalgia[27] and osteoarthritis[28] have demonstrated that the implementation of a PA program can be an effective intervention for treating kinesiophobia.

Furthermore, people with hEDS/G-HSD commonly report pain and muscle soreness, and the research herein describes both these symptoms as influential for PA participation. Despite the potential benefits of light stretching and foam rolling for these symptoms,[29] very few participants did these activities. Even though participants indicated good knowledge on symptom prevention and treatment, these results suggest that there may be a knowledge gap in participants, or other mechanistic barriers to PA (e.g., determent of stretching by healthcare providers).

4.2 Considerations for PA Research in hEDS/G-HSD

4.2.1 Diagnosis

While some limitations can be mitigated, others cannot given the nature of the research. Firstly, the inconsistencies in diagnostic criteria and recruitment methods for the studies mentioned in Chapter 2 can reduce the validity and comparability of the research. The most current diagnostic criteria for hEDS and G-HSD uses the International Classification of the Ehlers-Danlos Syndromes released in 2017, succeeding the 1988 Berlin, 1998 Villefranche and 1998 Brighton criteria.[30] Studies assessing PA as an intervention in people with hEDS/G-HSD date back to the 2000s when the nosology differed from today's. As a result, study samples may lack comparability on the basis of the different diagnostic criteria used, especially in studies employing multiple nosologies. This issue carries over to any other study recruiting participants diagnosed across time, hence can decrease the validity of the research as outdated criteria may not have identified a true hEDS/G-HSD diagnosis.

This issue is enhanced by using self-reported diagnoses in Chapter 3 as per the research herein. Recruitment using self-reported diagnoses is inexpensive, and can reach a higher number of participants, although it is not without its downfalls. Validity can be diminished in a study using self-reported diagnoses as these may differ from medical record diagnoses. This discrepancy can

be caused by limited health literacy, poor communication between patients and healthcare providers, self-diagnosis, or simply recall bias for those diagnosed anciently.

Furthermore, those who seek a diagnosis are more likely to be on the right side of the disease spectrum, where phenotypes are severe. General practitioners do not diagnose hEDS or G-HSD and mostly refer a suspected patient out to a specialist (i.e., geneticist, rheumatologist). In order for a referring physician to suspect the disease and the specialist to accept a consultation with a patient, the phenotype must meet a certain threshold to warrant suspicion of hEDS/G-HSD. Those on the mild side of the spectrum may trigger a suspicion of disease. Also, referring physicians must have the knowledge to refer, and specialists, to diagnose patients. Unfortunately, many do not, hence patients that receive a diagnosis often have access to healthcare from hEDS/G-HSD-knowledgeable specialists, which are uncommon.[31] As a result, a research sample may not be representative of the hEDS/G-HSD population.

4.2.2 PA Research

Studying PA can inherently introduce bias into research. First off, validity during between-study comparisons is difficult as published trials have inconsistent study designs – pre-post, non-randomized, controlled, single- or double-group trials and non-blinded trials. When conducting a randomized controlled trial to assess the effects of a PA intervention, blinding of participants is virtually impossible and introduces a challenge for minimizing detection and performance bias. Studying PA in a population with hEDS/G-HSD can be especially difficult as these individuals are prone to symptom aggravation, flare-ups, injury and other comorbidities. This vulnerability can highten the likelihood of dropout in clinical trials during long-term follow-ups, which in turn reduces the results' validity. In currently published trials, six studies reported on the presence of dropouts, many of which were due to flare-ups in their health.[2,3,9,10,32,33] Toprak Celenay et al. (2020) reported a higher-than-anticipated dropout rate at 17% and explicitly stated to consider dropouts when conducting trials in hEDS/G-HSD.[32]

Beyond this, current trials report on key outcomes using different measures. This causes issues for comparability between trials and renders making conclusions difficult. Some studies reported on a single outcome measure using multiples methods (i.e., questionnaires), and while this can increase the likelihood of comparability, resources used to consider these different assessment tools may be better used evaluating other outcomes. Ideally, a consensus on a single valid and reliable measure for each outcome in hEDS/G-HSD PA trials should be made to increase comparability. In addition, body area of study and PA program logistics varied widely across trials. This introduces strong heterogeneity in a review as joints and muscles may react to a certain PA differently, and similarly, different PA program can affect the body dissimilarly. While an overall conclusion may be made, it is difficult to pin-point the most effective program and to accurately determine its effects.

Moreover, it is difficult to accurately determine PA levels in any population. Social desirability bias can be present in both self-reported measures as well as objective measures, resulting in higher than actual levels of PA participation and decreased validity. Similarly, true PA levels may not be reported when using a survey which introduces response bias. To demonstrate, a study comparing PA participation between the Physical Activity Adult Questionnaire and accelerometery in Canadians identified an average of a 26-minute-per-day overestimation in the former compared to the latter, with only about 50% of the sample having a difference equal or less than 12.5 minutes per day.[34] Accurately estimating duration of PA can be further challenged in people with hEDS/G-HSD as their condition can vary largely from one day to the next due to flare-ups, symptom aggravation and injury, and their introspective ability may not be adequate. In addition, this population often has comorbidities that affect the autonomic system, namely postural orthostatic tachycardia syndrome. This condition can make mundane and low-energy-requiring activities such as a sit-to-stand movement spike the heart rate up to a higher-than-normal zone,[35] and render “moderate” and “vigorous” PAs difficult to quantify in this population.

4.3 Importance and Future Research

Regardless of the limitations, this work was crucial and filled a knowledge gap in the current hEDS/G-HSD literature. This work summarized the current PA intervention trials in people with hEDS/G-HSD and was able to provide a more definite conclusion on PA's advantages for symptom prevention and management. It also determined that by adopting a physically active lifestyle consisting of muscle-strengthening work, individuals with hEDS/G-HSD can alleviate the burden of these disorders and increase their overall health. Despite these benefits, current research reports low PA participation in populations with hEDS/G-HSD.

Understanding the factors that influence PA participation and their degree of influence in hEDS/G-HSD may contribute to increasing PA levels by informing the development of an effective and targeted intervention. More specifically, a program that provides education on the hEDS/G-HSD-specific and general benefits of PA and how to exercise safely as well as a program adapted to individual and population capabilities, may be a suitable intervention to mitigate barriers and improve PA levels in people with hEDS/G-HSD. While it is important for clinicians to consider patient needs individually, it can be difficult to collect all relevant information (i.e., patient priorities, PA-discouraging symptoms, functional capacities, accessibility to recreational environments, time restrictions) linked to PA participation in a single consultation. Hence, the barriers and facilitators to PA participation identified by our survey can better inform healthcare providers with knowledge they might not currently get during consultations with their patients. This can encourage the promotion of more individualized and hEDS/G-HSD-specific recommendations for PA, and in turn may improve adherence, and reduce disorder and healthcare burden.

Future work should use accelerometry and other objective measures to determine the predictors to PA participation in different sub-sections of people with hEDS/G-HSD (i.e., mild versus severe disease). Furthermore, prospective research should trial an intervention aimed at elevating PA levels in hEDS/G-HSD, and assess outcomes of long-term PA adherence. Additionally, clinical trials

considering all important outcomes should be performed to explore PA's effects on other commonly experienced hEDS/G-HSD symptoms.

4.4 Conclusion

This thesis assessed the effects of PA on various hEDS/G-HSD-relevant outcomes, as well as the PA behaviours, barriers and facilitators of people with hEDS/G-HSD. Results suggest PA leads to improvements in joint stability, muscle strength and endurance as well as many commonly experienced symptoms. Regardless, PA participation levels were low, especially of the vigorous and muscle-strengthening types, and barriers were widespread. This suggests a need for an intervention to reduce the impact of barriers and increase PA in this population. Future work should develop such an intervention and assess the impact of long-term PA adherence in people with hEDS/G-HSD. Enabling self-management through PA can not only reduce the burden of hEDS/G-HSD symptoms and disability, but also improve quality of life and overall wellness.

4.5 References

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