Exploring Pain, Fatigue, and Physical Activity in Adolescents with Hypermobility Spectrum Disorder or Hypermobile Ehlers–Danlos Syndrome

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All human beings are members of one frame,
Since all, at first, from the same essence came.
When time afflicts a limb with pain
The other limbs at rest cannot remain.
If thou feel not for other's misery
A human being is no name for thee.

Saadi Shirazi (1210–1292), Persian Poet

Abstract

Exploring Pain, Fatigue, and Physical Activity in Adolescents with Hypermobility Spectrum Disorder or Hypermobile Ehlers–Danlos Syndrome

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Abstract

Adolescents with Hypermobility Spectrum Disorder (HSD) and hypermobile Ehlers–Danlos Syndrome (hEDS) — two overlapping hereditary connective-tissue disorders characterized by joint hypermobility, chronic pain, impaired body perception, and musculoskeletal symptoms — are the primary focus of this doctoral thesis.

Aim: The aim was to better understand pain and its impact on function in activities of daily living in adolescents with HSD/hEDS.

Participants: This thesis comprises four studies conducted with three different cohorts of adolescents, including a total of 147 participants. Each cohort consisted of a group of adolescents with HSD/hEDS and a control group of healthy adolescents, in total 67 adolescents with HSD/hEDS and 80 healthy adolescents.

Methods: Hypermobility was assessed using the Del Mar Scale (Study I) and the Beighton Scale (Studies II–IV). Balance was evaluated with the Bruininks–

Oseretsky Test of Motor Proficiency (Study I). Participation in activities of daily living was measured with the Frequency of Participation Questionnaire, while pain and physical activity were recorded in a diary (Study I). Features of central sensitization, including primary and secondary hyperalgesia, endogenous pain modulation, and exercise-induced hyperalgesia, were measured through experimental pain assessments (Studies II and III). Levels of physical activity were objectively measured using an Axivity AX3 triaxial accelerometer, and sleep patterns were collected with an activity–sleep diary (Study IV). Fatigue was evaluated using the Pediatric Quality of Life Inventory — Multidimensional Fatigue Scale, and pain catastrophizing was assessed with the Pain Catastrophizing Scale — Child version (Studies III and IV).

Results: In Study I, it was found that adolescents with HSD/hEDS had significantly more joint hypermobility, experienced greater pain, scored lower on balance tests, and were more affected in their activities of daily living, compared with the control group. Study II demonstrated the feasibility of using experimental pain measurements to investigate underlying pain mechanisms, particularly central sensitization. Study III applied these methods, showing increased general pain sensitivity and a partially reduced pain-inhibitory effect of exercise in adolescents with HSD/hEDS. In Study IV, it was found that adolescents with HSD/hEDS devoted significantly more time to sedentary behavior and less time to moderate-to-vigorous physical activity, and exhibited more nighttime movement, compared with the control group. However, no association was found between fatigue and these activity patterns when pain catastrophizing was controlled for.

Conclusions: This thesis highlights that adolescents with HSD/hEDS are significantly impacted in their daily lives, especially in terms of pain, physical activity, and restricted participation in everyday activities. The research suggests a potential connection between HSD/hEDS and central sensitization. It suggests that pain should be understood as a complex issue influenced by central sensitization and biopsychosocial factors. Further, the thesis shows that adolescents with HSD/hEDS are less physically active and exhibit more sleep movements than the control group, which highlights the need for better physical-activity and sleep-health interventions in adolescents with HSD/hEDS. Future research should aim at developing targeted treatments to improve physical activity and alleviate pain in adolescents with HSD/hEDS.

Keywords: Hypermobility, pain, adolescents, central sensitization, physical activity, participation, fatigue, Hypermobility Spectrum Disorder, hypermobile Ehlers–Danlos Syndrome

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Sammanfattning

Sammanfattning på svenska

Ungdomar med överrörliga leder och smärta, det vill säga symtomatisk hypermobilitet (mer specifikt: hypermobilitetsspektrumstörning eller hypermobilt Ehlers–Danlos syndrom (HSD/hEDS)), har visats vara en patientgrupp som återfinns i många olika kliniska verksamheter. Trots framsteg inom forskningen har man ännu inte identifierat de underliggande faktorer som bidrar till att vissa ungdomar med hypermobilitet drabbas av svår smärta samtidigt som andra förblir relativt opåverkade.

Det övergripande syftet med denna avhandling var att få en bättre förståelse för bakomliggande faktorer till smärtan och dess inverkan på livet. Mer specifikt jämförs ungdomar med HSD/hEDS och friska ungdomar avseende eventuellt ökad förekomst av känslighet för provocerad smärta (som ett mått på central sensitisering), och ungdomarnas aktivitetsnivåer och fysiska förmåga jämförs.

Avhandlingen består av fyra studier som genomfördes med tre olika undersökningsgrupper. Varje undersökningsgrupp består av en grupp ungdomar med HSD/hEDS och en kontrollgrupp av friska ungdomar i samma ålder. Ungdomarnas ledöverrörlighet, balans, smärtkänslighet och aktivitetsnivåer undersöktes. Deltagarna svarade även på enkäter om deltagande i dagliga aktiviteter, trötthet och katastroftankar om smärta.

Resultaten visade en potentiell koppling mellan HSD/hEDS och central sensitisering, som påverkade den smärtlindrande effekten av träning negativt. Dessutom var ungdomar med HSD/hEDS mindre fysiskt aktiva, mindre delaktig i mer fysiskt krävande aktiviteter och rörde sig mer under sömnen i jämförelse med kontrollgruppen.

Slutsatser: De fyra studierna i denna avhandling ger en omfattande bild av de utmaningar som ungdomar med HSD/hEDS ställs inför. Smärta bör förstås som ett komplext fenomen påverkat av central sensitisering och biopsykosociala faktorer. Avhandlingen pekar på ett behov av bättre insatser för fysisk aktivitet och sömnhälsa för dessa ungdomar. Framtida forskning bör inriktas på att utveckla personcentrerade behandlingar för att förbättra fysisk aktivitet och lindra smärta hos ungdomar med HSD/hEDS.

Zusammenfassung

Zusammenfassung auf Deutsch

Jugendliche mit überbeweglichen Gelenken und Schmerzen, symptomatische Hypermobilität (genauer gesagt: Hypermobilitäts-Spektrum „Disorder“ oder hypermobiles Ehlers-Danlos-Syndrom (HSD/hEDS)), sind zunehmend eine zu beachtende Patientengruppe im klinischen Alltag geworden. Forschung hat gezeigt, dass diese Jugendlichen eine signifikante Beeinträchtigung ihres täglichen Lebens erfahren. Trotz wissenschaftlicher Fortschritte sind die zugrunde liegenden Faktoren, die erklären, warum manche Jugendliche mit HSD/hEDS starke Schmerzen entwickeln, während andere relativ unbeeinflusst bleiben, noch nicht identifiziert worden.

Das übergeordnete Ziel dieser Dissertation war es, ein besseres Verständnis für die zugrunde liegenden Faktoren für Schmerzen und deren Auswirkungen auf das Leben für Jugendliche mit HSD/hEDS zu erlangen. Spezifischer wurden Jugendliche mit HSD/hEDS und gesunde Jugendliche in Bezug auf eine möglicherweise erhöhte Empfindlichkeit gegenüber provozierten Schmerzen (als Maß für die sogenannte zentrale Sensibilisierung) sowie die Aktivitätsniveaus und die körperliche Leistungsfähigkeit der Jugendlichen verglichen.

Die Dissertation besteht aus vier Studien, die mit drei verschiedenen Untersuchungsgruppen durchgeführt wurden. Jede Untersuchungsgruppe besteht aus einer Gruppe Jugendlicher mit HSD/hEDS und einer Kontrollgruppe gesunder Jugendlicher im gleichen Alter. Untersucht wurden die Gelenküberbeweglichkeit, das Gleichgewicht, die Schmerz-empfindlichkeit und die Aktivitätsniveaus der Jugendlichen. Die Teilnehmer beantworteten zudem Fragebögen über die Teilnahme an täglichen Aktivitäten, Müdigkeit (Fatigue) und katastrophisierende Gedanken über Schmerz.

Die vier Studien dieser Dissertation bieten ein umfassendes Bild der Herausforderungen, denen Jugendliche mit HSD/hEDS gegenüberstehen, insbesondere in Bezug auf Schmerzen, Müdigkeit (Fatigue), körperliche Aktivität und die Teilnahme am täglichen Leben. Die Ergebnisse weisen auf einen potenziellen Zusammenhang zwischen HSD/hEDS und zentraler Sensibilisierung hin, was die schmerzlindernde Wirkung von Bewegung

negativ beeinflusste. Schmerzen sollten als komplexes Problem verstanden werden, das durch zentrale Sensibilisierung und biopsychosoziale Faktoren beeinflusst wird. Die Ergebnisse zeigten auch, dass Jugendliche mit HSD/hEDS tagsüber weniger körperlich aktiv waren und sich während des Schlafs intensiver bewegten als die Kontrollgruppe. Dies unterstreicht die Notwendigkeit besserer Maßnahmen zur Förderung der körperlichen Aktivität und der Schlafgesundheit bei diesen Jugendlichen. Zukünftige Forschung sollte sich darauf konzentrieren, gezielte Behandlungen zu entwickeln, um die körperliche Aktivität zu verbessern und Schmerzen bei Jugendlichen mit HSD/hEDS zu lindern.

List of papers

Contents

Abbreviations

Definitions

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Schubert-Hjalmarsson E, Ohman A, Kyllerman M, Beckung E. **Pain, Balance, Activity, and Participation in Children with Hypermobility Syndrome.** Pediatr Phys Ther. 2012;24(4):339–44.

II. Schubert-Hjalmarsson E, Fasth A, Ickmans K, Mårdbrink E-L, Söderpalm A-C, Lundberg M. **Central sensitization in adolescents with hypermobility spectrum disorder or hypermobile Ehlers-Danlos syndrome—a feasibility study.** Pilot Feasibility Stud 2023;9(1):97–106.

III. Schubert-Hjalmarsson E, Fasth A, Ickmans K, Mårdbrink E-L, Söderpalm A-C, Lundberg M. **Exploring Signs of Central Sensitization in Adolescents with Hypermobility Spectrum Disorder or Hypermobile Ehlers-Danlos Syndrome.** Accepted in European Journal of Pain, October 2024, DOI:10.1002/ejp.4754

IV. Schubert-Hjalmarsson E, Fridolfsson J, Arvidsson D, Börjesson M, Lundberg M. **Physical activity patterns in adolescents with hypermobility related disorders.** In manuscript

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Abbreviations

CS	Central sensitization
EIH	Exercise-induced hypoalgesia
HADS	Hospital Anxiety and Depression Scale
hEDS	Hypermobile Ehlers–Danlos Syndrome
HSD	Hypermobility Spectrum Disorder
PCS-C	Pain Catastrophizing Scale — Child version
PedsQL-F	Pediatric Quality of Life Inventory — Multidimensional Fatigue Scale, child version
PPT	Pressure-pain threshold

Definitions in short

Central sensitization	"An amplification of neural signaling within the central nervous system that elicits pain hypersensitivity"[1].
Fatigue	"An overwhelming sense of tiredness, lack of energy, and feeling of exhaustion, which is not the same as muscle weakness"[2].
Joint hypermobility	Joint hypermobility refers to the ability of an individual to move one joint or a group of joints, passively and/or actively, beyond the expected range of motion[3].
Movement behavior	Movement behavior encompasses the range of physical activities and sedentary actions that an individual engages in throughout daily life. This includes all forms of physical activity, from structured exercise and recreational activities to everyday tasks, as well as periods of inactivity or sedentary behavior[4, 5].
Physical activity	"Any bodily movement produced by skeletal muscles that requires energy expenditure"[4].
Physical exercise	"Physical activity that is planned, structured, and repetitive and has the improvement or maintenance of physical fitness as a final or intermediate objective"[4].

Preface

Preface

Since 2003, children and adolescents with hypermobility-related problems have come to me in my professional role as a physiotherapist at the Queen Silvia Children's Hospital in Gothenburg, Sweden. They presented with symptoms such as pain and fatigue that affected their daily lives and their ability to be physically active. Throughout this time, scientific knowledge has not been sufficient to enable me or my colleagues to fully understand the impact of hypermobility nor to address the problems that arose owing to hypermobility in these children's and adolescents' daily lives. There was a gap in the literature regarding the course and treatment of individuals with hypermobility, especially for children and adolescents. The generally preferred management options, originally based on biomechanical explanatory models, included recommended restrictions to physical activity. To reduce the risk of injury, contact sports as well as activities involving jumping, climbing, or hanging from rings were not allowed.

However, some children and parents challenged these recommendations. Together, we observed that jumping on a trampoline or engaging in other sporting activities made some children reach a higher level of functioning while others instead experienced more pain and became more inactive.

It was at this point that my interest in understanding more about the diagnosis was piqued. This led me and a few colleagues to conduct a first study to make an inventory of some characteristics of this group. However, the results left us with more questions than we had before. It remained unclear why some adolescents with joint hypermobility experience more difficulties than others, and why the amount and characteristics of their pain do not seem to be related to their degree of hypermobility.

Then I set out on an intensive journey, immersing myself in existing knowledge and challenging myself to rethink and develop new ideas. There has been significant progress in research on this syndrome, and I have learned a lot from other people's research, international workshops, and contacts — and, above all, from all the patients I had the privilege to meet and follow. Many of their stories motivated me to continue this journey, which has now culminated in this thesis.

My hope is that my research can uncover a small piece of the puzzle of understanding this diagnosis better, support the development of evidence-based treatments, and thereby improve the care of children and adolescents with Hypermobility Spectrum Disorder and hypermobile Ehlers–Danlos Syndrome.

Introduction

Introduction

Hypermobility Spectrum Disorder (HSD) and hypermobile Ehlers–Danlos Syndrome (hEDS) are two complex multisystemic conditions that lack a clear affiliation within the Swedish healthcare system. Patients with HSD/hEDS struggle for acknowledgment of their symptoms, which are often difficult to interpret[6, 7]. Instead of receiving continuous and cohesive care, patients are cross-referred between healthcare units[8]. As a result, they are forced to navigate the healthcare system on their own. They often feel mistrusted and questioned in their interactions with healthcare providers[6]. Considering the relatively high prevalence of 1 in 5,000[9], it is likely that there is a significant number of undiagnosed individuals. Studies have shown that the average time to receive a diagnosis is more than ten years, which increases the risk of improper care, mismanagement of symptoms, and poor access to knowledgeable healthcare providers such as physiotherapists, occupational therapists, and psychologists[6]. The emotional overlay of medical neglect, combined with acute and chronic injuries, leaves these patients vulnerable to more complex pain experiences with accompanying physical difficulties.

The main symptoms in these overlapping conditions are chronic pain and fatigue, which lead to great suffering for the individuals and their families, produce substantial long-term consequences, and significantly impact physical activity and physical function[10]. Understanding the underlying mechanisms of the pain and the impact of the fatigue is crucial for planning therapeutic interventions and comprehending what the individual's everyday life is like. In fact, being physically active is a key prerequisite for participation in everyday life, and one of the United Nations' major global-development goals is precisely to promote health worldwide by encouraging physical activity[11].

Physiotherapy fundamentally involves assessing, diagnosing, and treating movement and functional impairments to enhance individuals' quality of life. It integrates evidence-based practices and patient-centered approaches to improve physical function, alleviate pain, and prevent injuries[12]. Since exercise is one of the cornerstones of physiotherapy treatment and multimodal pain management, understanding the underlying pain mechanisms and their impact on physical activity is essential. The present

research project offers valuable insights that help deepen our understanding of these areas, potentially improving treatment outcomes and causing functional impairments to be more effectively addressed.

Adolescence

This thesis is about adolescents with HSD/hEDS. Adolescence — which is derived from the Latin verb *adolescere*, meaning 'to grow up' — is the period between childhood and adulthood, defined by the World Health Organization (WHO) as ages 10 to 19[13] [A]. Puberty, which marks the onset of adolescence, involves significant physical, cognitive, emotional, and social changes[14]. Pubertal hormones also contribute to brain maturation[15]. More recently, under the influence of various both biological and social factors, the period of adolescence has grown longer owing to earlier puberty onset and delayed adult roles[16].

During adolescence, individuals experience insecurity about their bodies and about their personal identity, which is in a formative period[17]. This phase includes physical development (with girls' physical growth slowing around age 15–19 years while boys continue to grow until around age 20–24 years) as well as an increase in abstract thinking, goal-setting, and moral reasoning[17]. Emotional and social development also occurs during this phase, involving a strengthened identity, independence from parents, deeper peer relationships, and interest in romantic relationships; this development can continue far beyond the point when physical growth has finished, up to 24 years of age[17]. It should be noted that sociocultural contexts significantly affect adolescents' developmental expectations and experiences[17].

To navigate these developmental transformations successfully, adolescents need a supportive environment and personal resources. Moreover, adolescence lays the foundation for good health in that it offers opportunities

[A] Throughout this thesis, all participants will be referred to as adolescents, even though some of them are slightly outside the age range given here.

to establish future health patterns[17, 18]. However, this period is also marked by increased health problems, including with pain and mental health[17, 19].

For adolescents with joint hypermobility, these changes in the body and mind throughout puberty may lead to the onset of, or an increase in, symptoms such as pain and fatigue.

Joint hypermobility

Definitions and classifications

Joint hypermobility refers to the ability of an individual to move one joint or a group of joints, passively and/or actively, beyond the expected range of motion[3, 20]. In addition to the increased range of motion, joint instability may also occur but does not necessarily result from joint hypermobility[3]. It should be noted that this is more of a description than a diagnosis[3]. A person's joint mobility depends on various factors such as age, sex, ethnic background, and training[21]. Children are typically more mobile than adults, and women more mobile than men. Joint hypermobility is part of the normal variation and occurs in approximately 20–30 percent of children and adolescents[22, 23]. In and of itself, joint hypermobility does not necessarily lead to any symptoms, but it does entail an increased risk of becoming symptomatic over time[24, 25].

Even in the fourth century B.C., Hippocrates characterized joint hypermobility as an ailment that requires intervention[26]. During the late 1800s and early 1900s, the signs and symptoms described in early case reports were compiled and attributed to diagnoses in the scientific literature[27-30]. In the 1960s, the term “hypermobility syndrome” was introduced for cases where otherwise healthy (normal) individuals with joint laxity presented with musculoskeletal complaints[20]. However, there was some terminological confusion between medical specialties: rheumatologists used the term “joint hypermobility syndrome”[27], while geneticists and dermatologists used the term “Ehlers–Danlos Syndrome”[31]. Recently, specialists in these fields have recognized that there is an overlap between these diagnoses[3, 32, 33], and agreement was reached in 2017 on the terminology to be used about the specific diagnoses of HSD and hEDS[3, 34, 35].

Over the years, various terms have thus been used to describe the same phenomenon (Table 1). This terminological diversity is due to the fact that different research groups and specialists encountered and named the phenomenon independently. To facilitate communication between healthcare providers, Castori et al.[3] defined different types of joint hypermobility (Table 1). From now on in this thesis, the term HSD will be used to refer to any symptomatic joint hypermobility that does not meet the criteria for hEDS.

Table 1. Terminology to describe joint hypermobility

Terminology before 2017	**Abbreviation**	**Definition**
Joint hypermobility	JH	Hypermobility without symptoms
Generalized joint hypermobility	GJH	Generalized hypermobility without symptoms
Joint Hypermobility Syndrome	JHS	Hypermobility with symptoms such as pain
Beighton Joint Hypermobility Syndrome	BJHS	Hypermobility with symptoms such as pain
Joint laxity disorder		Hypermobility with symptoms such as pain
Inherited connective-tissue laxity/disorder		Hypermobility with symptoms such as pain
Terminology after 2017	Abbreviation	Definition[3]
Local joint hypermobility	LJH	Hypermobility in one or a group of joints
Peripheral joint hypermobility	PJH	Hypermobility limited to hands and/or feet
General joint hypermobility	GJH	Assessed according to the Beighton Scale; different cutoffs for different age groups
Historical joint hypermobility	HJH	Previously hypermobility, no longer present owing to age or injuries

Joint hypermobility can cause symptoms and may then be diagnosed as HSD or hEDS[3]. Additionally, it can be listed as a symptom in various rarer diagnoses such as other subtypes of Ehlers–Danlos Syndrome, Marfan Syndrome, Osteogenesis Imperfecta, 22q11 Deletion Syndrome, and others[3,

[34, 36]. Figure 1 schematically represents this progression, highlighting the transitions between phenotypes as well as the broad range of comorbidities related to joint hypermobility that may affect all stages from HSD to hEDS[3].

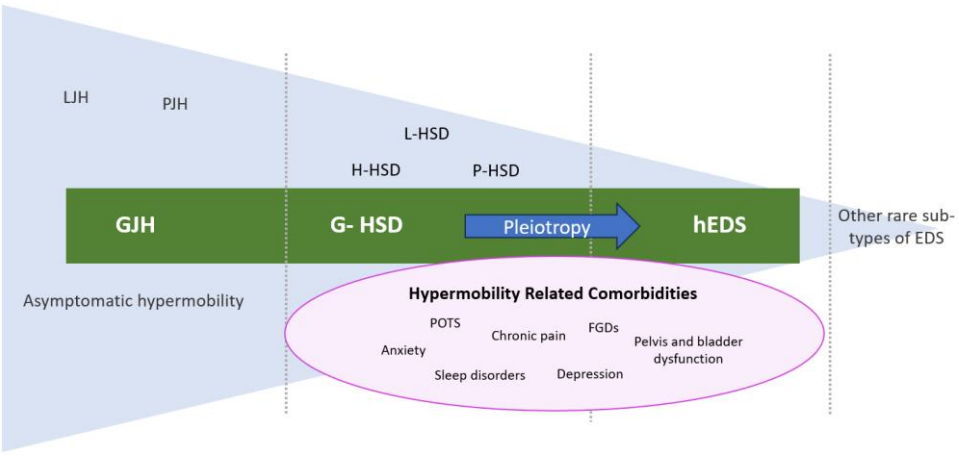


Figure 1. 2017 classification — a continuum of Hypermobility Spectrum Disorder (HSD), hypermobile Ehlers–Danlos Syndrome (hEDS), and rarer types of Ehlers–Danlos Syndrome (EDS).

Schematic representation of the continuum of hypermobility from asymptomatic hypermobility over HSD and hEDS to other rare subtypes of EDS. The light blue triangle represents prevalence within the hypermobility paradigm as well as domains within hypermobility. The green rectangle represents the transitions from generalized hypermobility to hEDS. The pink oval shows the broad range of comorbidities related to joint hypermobility that may occur in all the phenotypes from HSD to hEDS. The vertical lines represent the transitions between the different conditions.

Abbreviations: LJH = Local joint hypermobility; PJH = Peripheral joint hypermobility; GJH = General joint hypermobility; L-HSD = Localized Hypermobility Spectrum Disorder, H-HSD = Historical Hypermobility Spectrum Disorder; P-HSD = Peripheral Hypermobility Spectrum Disorder; G-HSD = Generalized Hypermobility Spectrum Disorder; hEDS = hypermobile Ehlers–Danlos Syndrome; EDS = Ehlers–Danlos Syndrome (various types); POTS = Postural Orthostatic Tachycardia Syndrome; FGDs = functional gastrointestinal disorders.

Pleiotropy is a genetic phenomenon whereby a single gene affects multiple phenotypic traits or characteristics of an organism. This means that a mutation in a single gene can lead to changes in several different biological processes or structures[3, 34].

Identifying joint hypermobility

Since joint hypermobility is one of the first indicators for diagnosing HSD/hEDS, it is important to know how to identify joint hypermobility.

The range of motion of a joint can be assessed with an instrument called a goniometer. Standardized normal values for age and sex have been developed for joint-mobility measurement points and positions that are used in clinical settings[37].

To identify generalized hypermobility, the goniometer is used in combination with standardized scales. One of these scales is the Beighton Scale, which was initially developed for epidemiological studies but has since been established as the gold standard for assessing generalized hypermobility, particularly in the context of HSD and hEDS, where it is now widely used for diagnostic purposes[38, 39]. The Beighton Scale has cutoff values for children, adults, and adults older than 50 years[39]. Another scale used to identify generalized hypermobility is the Del Mar Scale[40]. It includes the measurements of the Beighton Scale and adds four additional joint assessments; it has a cutoff value for adults. Both scales are described in detail in the section entitled "Assessment of joint hypermobility" on page 48 of this thesis.

Further, in a clinical setting, given that the Beighton Scale focuses on only a few joints in the upper and lower extremities, the Upper Limb Hypermobility Assessment Tool and the Lower Limb Assessment Score both provide valuable information for planning treatment interventions. These tools will not be further described here but are discussed elsewhere[41, 42].

Ehlers–Danlos Syndrome

Ehlers–Danlos Syndrome (EDS) encompasses 13 types of hereditary connective-tissue disorders, all but one of which have a known genetic basis[34]. The focus of this thesis is on hypermobile EDS (hEDS), the only type

currently lacking a known genetic association and thus diagnosed based on clinical symptoms[3, 34].

A. Tschernogubow [B], a Russian dermatologist, wrote the first medical record of EDS in 1891[43]. It was not until the 1930s that the syndrome was given its current name, which was inspired by the descriptions made by Edvard Ehlers, a Danish dermatologist (1863–1937), and Henri Alexandre Danlos, a French physician (1844–1912)[44-46]. Diagnostic criteria for the various types of EDS were first standardized and clarified in 1988[47]. These types were originally designated by Roman numerals based on clinical and hereditary factors. In 1998, new criteria were established and presented in the Villefranche Classification to categorize the different types of EDS[48]. At the same time, the Brighton Criteria were established to diagnose joint hypermobility syndrome[32]. The Villefranche Classification remained in use for almost two decades. In 2017, an update yielded the current classification system for EDS, with 13 types based on clinical features and their genetic background along with a revised nomenclature[34] (Appendix 1).

The classification of EDS is a dynamic process, evolving in line with an increasing scientific understanding and the identification of new types of EDS. We can thus expect new revisions and updates to the classification as research continues to advance.

Hypermobile Ehlers–Danlos Syndrome

Hypermobile Ehlers–Danlos Syndrome (hEDS) is the most common type of EDS, with a prevalence of 1:5,000[9], and is characterized by generalized joint hypermobility, skin extensibility, and tissue fragility presumed to be caused by disease causing variant(s) in a gene that affects the collagen structure[35]. The molecular defect behind hEDS is still unknown[34]. The pathogenetic events underlying hEDS are located in the connective tissue, specifically in collagen, a structural-protein molecule that is a main component of connective tissue[49]. The primary physical characteristics of connective tissue are its great strength and relative inextensibility. Because of these

[B] Chernogubov in English transcription

characteristics, connective tissue provides good support for the extracellular matrix of tendons, ligaments, fascia, dermis, bone, blood vessels, and most other tissues[49]. The molecular defects underlying hEDS disrupt the formation of the biochemical structure of collagen and impair its physical properties. This leads to laxity, fragility, and mechanical failure[21]. hEDS is inherited in an autosomal dominant manner and is more common in females[34, 48].

Under the diagnostic criteria from 2017, three main criteria must be met for an hEDS diagnosis to be made. Criterion 1 is generalized joint hypermobility according to the Beighton Scale. Criterion 2 actually consists of three alternative criteria: 2A) at least 5 out of 12 systemic manifestations of more generalized connective-tissue symptoms; 2B) positive family history in first-degree relatives; and 2C) at least one musculoskeletal complication such as chronic musculoskeletal pain. Criterion 3 involves the exclusion of alternative diagnoses that may also include joint hypermobility[34]. For example, muscle hypotonia can indicate muscle diseases[50], and hEDS can also be mistaken for rheumatic pain[51].

The symptoms of hEDS can vary between individuals, even within the same family[3]. Because hEDS is a symptomatic diagnosis, the risk of misdiagnosis is high. In addition, the diagnostic process tends to be slow. As mentioned before, it has been shown to take an average of more than ten years for individuals with hEDS to receive a diagnosis[6]. It is believed that HSD and hEDS constitute one and the same condition[3, 32]. Individuals within a family who have this condition may be given different diagnoses depending on the symptoms exhibited by them[3]. What is more, the same individual's diagnosis may change over time as the symptom profile evolves (and as research progresses).

Children rarely meet all physical diagnostic criteria. In fact, they often receive a diagnosis based on a first-degree relative having the condition. For this reason, a recommendation to be cautious and use a more descriptive nomenclature when diagnosing children and adolescents was issued in 2023[52].

Hypermobility Spectrum Disorder

Hypermobility Spectrum Disorder (HSD) is intended as an alternative diagnosis for patients with symptomatic joint hypermobility who do not present with a rare type of EDS nor meet the criteria for hEDS, for instance in terms of the severity or pattern of musculoskeletal involvement[3]. It is a descriptive diagnosis according to which individuals exhibit joint hypermobility and experience symptoms such as recurrent or chronic musculoskeletal pain, dislocations, and/or subluxations without trauma[3]. HSD manifests as pain in one or more joints or as generalized pain that may also be perceived as "wandering" throughout the body[3]. In addition, it can include a limited involvement of other organs and tissues, provided that the overall clinical picture of the individual's symptoms does not meet the criteria for any EDS type[3].

An HSD diagnosis can be applied to individuals who have a family history of hEDS but do not meet the hEDS criteria themselves. HSD is intended to span the gap between asymptomatic joint hypermobility and hEDS. To ensure a structured approach to the diagnosis and management of patients with issues related to joint hypermobility, that gap has been divided into four discrete HSD subtypes[3]:

Generalized HSD (G-HSD): Generalized joint hypermobility, assessed objectively with the Beighton Scale, plus one or more secondary musculoskeletal manifestations.

Peripheral HSD (P-HSD): Joint hypermobility limited to hands and feet plus one or more secondary musculoskeletal manifestations.

Localized HSD (L-HSD): Joint hypermobility at single joints or groups of joints plus one or more secondary musculoskeletal manifestations related to the hypermobile joint(s).

Historical HSD (H-HSD): Self-reported historical generalized joint hypermobility (previous hypermobility which is no longer present owing to age or injuries), with a negative Beighton score plus one or more secondary musculoskeletal manifestations. This diagnosis, which is assessed using the Five-Part Questionnaire on Hypermobility, is used only for adults[36, 53].

Comorbidity

Individuals with HSD/hEDS manifest a high frequency of comorbidities that significantly impact their quality of life and suffering[6, 54]. Comorbidity refers to the "combined effects of additional conditions in reference to an index disease"[55]. It can occur when a primary disease increases the risk of another disease, or when two diseases arise independently of each other. Comorbidity can affect the course, treatment strategies, and prognosis for a disease[56].

While not part of the diagnostic criteria for HSD/hEDS, comorbidity has a significant impact on everyday difficulties and quality of life for individuals with those diagnoses. Complaints more commonly seen in individuals with HSD/hEDS than in the general population include chronic widespread pain[6], fatigue[6], sleep disturbance[57], gastrointestinal issues[58, 59], urinary incontinence[60], allergies and immunological disorders (specifically mast-cell activation)[61], autonomic dysfunction (specifically Postural Orthostatic Tachycardia Syndrome (POTS))[62], anxiety and depression[24], and neuropsychological disorders such as Attention Deficit Hyperactivity Disorder (ADHD) and autism[63-65].

Pain

Chronic pain is one of the main symptoms in HSD/hEDS. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"[66]. Pain is an experience unique to each person, influenced by various biopsychosocial factors[66]. Hence pain cannot solely be explained as activity in sensory neurons and thus is a different phenomenon from nociception[66]. Chronic pain is "pain that lasts or recurs for longer than 3 months"[67, 68]. It can thus be either persistent or intermittent. Unlike acute pain, which typically resolves as the underlying

tissue heals, chronic pain continues beyond the expected period of recovery and can significantly impact an individual's daily functioning and overall quality of life[67].

Pain-processing pathways in the nervous system

Pain physiology, or the science of how pain is processed and perceived, involves a complex interaction between various neural and biochemical pathways (Figure 2). Nociception is the process by which sensory receptors called nociceptors detect harmful or potentially harmful stimuli (Table 2). Nociceptors are specialized neurons located throughout the body, particularly in the skin, joints, and internal organs. They respond to thermal, mechanical, and chemical stimuli[69]. When activated, nociceptors generate electrical signals that travel along peripheral nerves toward the spinal cord. This involves two types of nerve fibers: A-delta fibers, which are myelinated and transmit signals or action potentials quickly; and C-fibers, which are unmyelinated and transmit slowly[70]. Activation of A-delta fibers may potentially lead to sharp, precisely located pain while activation of C-fibers leads to dull, aching pain.

Once in the spinal cord, the electrical signals enter the dorsal horn, where they synapse with secondary neurons. Neurotransmitters such as glutamate and Substance P play important roles in transmitting the signals[71]. The spinal cord not only relays these signals to the brain but also modulates them via descending inhibitory pathways, which can either amplify or dampen the perceived intensity of pain, depending on context[72, 73]. Once the signals reach the brain, they are transmitted to various regions through the spinothalamic tract.

Key brain regions involved in pain perception include the thalamus, somatosensory cortex, limbic system, and prefrontal cortex[74]. The thalamus acts as a relay station, directing signals to the appropriate cortical areas for further processing. The somatosensory cortex is responsible for determining the location and intensity of pain, while the limbic system and prefrontal cortex are involved in the emotional and cognitive aspects of pain[75].

The brain can influence pain perception through descending pathways coming from regions such as the periaqueductal gray matter and the rostral ventromedial medulla. These pathways release endogenous opioids (such as endorphins) and other neurotransmitters (such as serotonin and norepinephrine) that inhibit signals at the spinal level[72, 73].

Pain is thus a complex phenomenon. A deeper understanding is needed to identify its various components, which influence each other and may therefore affect the outcome of treatment interventions[76].

Types of pain

Pain has been divided into nociceptive pain, which is the type described above, and neuropathic pain, which is pain caused by damage to or disease of the somatosensory nervous system[66]. In 2017, the IASP introduced a third category: nociplastic pain, which is pain that arises from altered nociception without clear evidence of tissue damage, meaning that there are now three mechanistic pain descriptors[66] (Table 2). More than one of these pain mechanisms can occur simultaneously in the same individual. Furthermore, ongoing nociceptive pain can be a risk factor for developing nociplastic pain. In individuals with predominant nociplastic pain[77, 78], both nociceptive pain and nociplastic pain can thus occur[79]. This may explain why widespread pain develops in individuals with HSD/hEDS: long-term nociceptive pain from hypermobile and unstable joints may cause nociplastic pain.

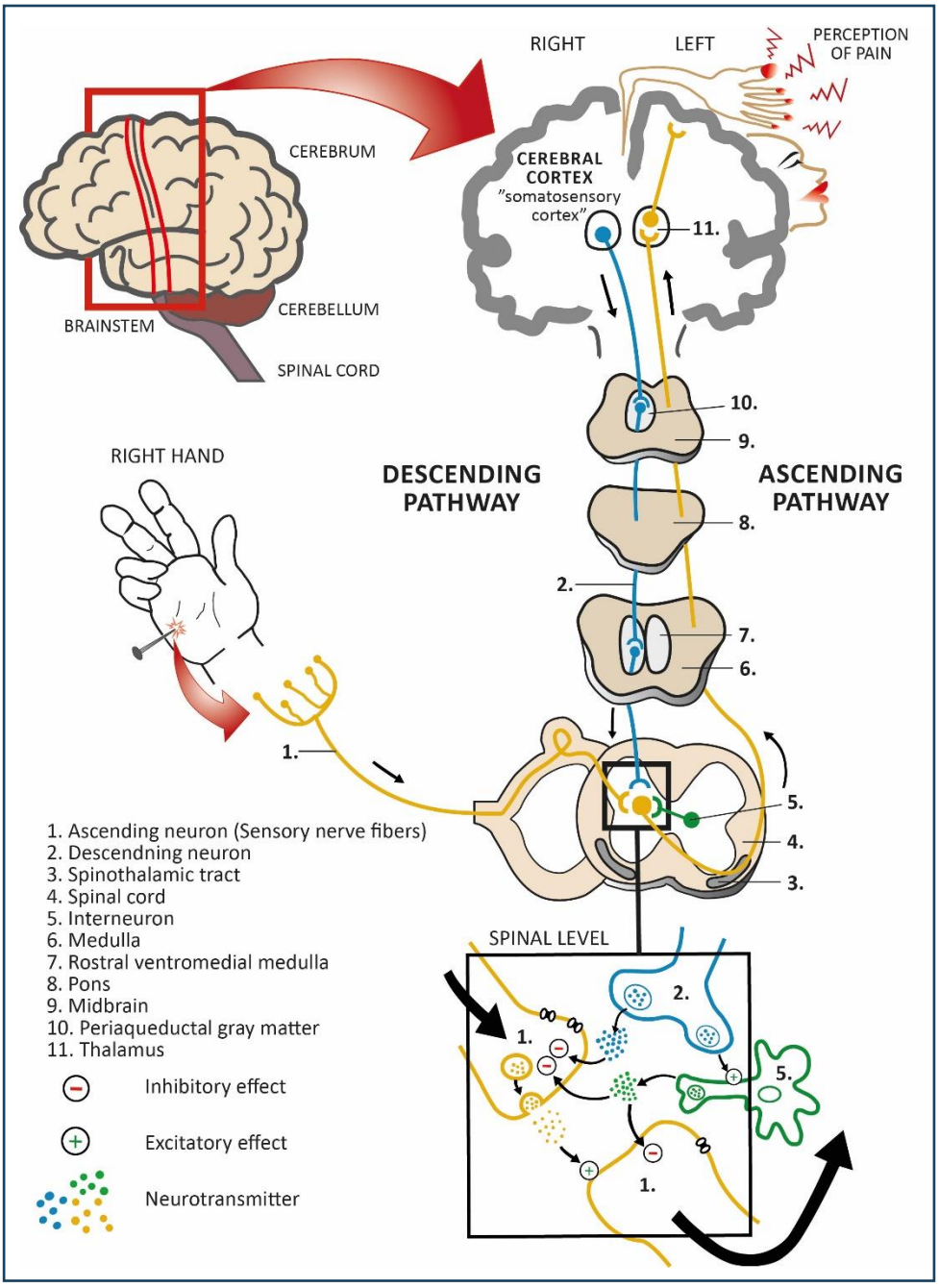


Figure 2. Schematic presentation of the nociceptive pain process.
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Table 2. Description of pain according to the International Association for the Study of Pain[66]

TYPES OF PAIN		
Nociceptive pain	**Neuropathic pain**	**Nociplastic pain**
Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors.	Pain caused by damage to or disease of the somatosensory nervous system.	Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors nor any clear evidence of damage to or disease of the somatosensory system causing the pain.

As already indicated, pain is not solely a physiological experience. Rather, it is profoundly influenced by psychological and social factors. Stress, anxiety, and depression can exacerbate pain perception, while a supportive social environment and effective coping strategies can mitigate it[76]. The biopsychosocial model of pain highlights the need for a comprehensive approach to pain management that addresses these multifaceted influences[80]. It is described in the section entitled "The Biopsychosocial Model" on page 29 of this thesis.

Central sensitization

Although the underlying mechanisms of chronic pain in adolescents with HSD/hEDS are unclear, central sensitization (CS) has been proposed as a possible explanation[81, 82]. In the case of chronic pain, neuroplastic changes in the nervous system can increase sensitivity to pain, even in the absence of ongoing injury or inflammation[83]. CS is widely considered a dominant mechanism in nociplastic pain conditions[84]. It refers to various central pain-enhancing processes, characterized by heightened sensitivity of the pain

system[85]. More broadly, CS is defined as the "amplification of neural signaling within the central nervous system that elicits pain hypersensitivity"[1], which includes not only spinal processes but also complex neuroplastic changes throughout the central nervous system[1, 86].

Traditionally, CS has been described as an amplification of pain signaling at the spinal level, particularly in the dorsal horn of the spinal cord, that occurs after injury or inflammation and leads to increased sensitivity[87]. This classical view focuses on local neuroplastic changes, where the overactivation of neurons in injured areas results in hyperalgesia and allodynia[87]. Recently, however, there has been a paradigm shift in the understanding and management of CS, emphasizing the role of pain modulation in the central nervous system[88, 89]. This has led to a shift in pain management away from focusing solely on peripheral mechanisms toward also paying attention to central mechanisms. This broader understanding of CS is also able to explain increased sensitivity to different sensory stimuli, such as touch, light, and sound, as well as widespread pain beyond the site of the initial injury[90]. Since CS can occur in both acute and chronic conditions, involving disturbances in both the ascending nervous system and the descending one, it is recommended to use multiple measurement methods in order to reliably detect signs of CS[91].

Adopting this broader definition of CS can yield a more comprehensive understanding of the sensory and pain-related changes in individuals with HSD/hEDS. This means that a more nuanced understanding of this condition can be obtained by measuring signs of CS. Such signs can be measured, for example, through assessment of primary and secondary hyperalgesia, endogenous pain modulation, and exercise-induced hypoalgesia, as described in the following section.

Pain sensitivity and modulation

Pain sensitivity can be assessed through the measurement of pressure-pain thresholds (PPTs) at both symptomatic and asymptomatic sites, corresponding to primary and secondary hyperalgesia, respectively. In symptomatic sites, reduced PPTs indicate primary hyperalgesia, which might

be due to sensitization of nociceptors in the affected peripheral musculoskeletal tissues[92]. Low PPTs at asymptomatic sites, further away from the symptomatic region, instead suggest secondary hyperalgesia.

Endogenous pain modulation refers to the central nervous system's capacity to reduce or amplify pain through various mechanisms[93]. For instance, signals originating from the brainstem can inhibit nociceptive signals at the spinal level[93, 94]. This process is often referred to as "pain inhibits pain," with one nociceptive stimulus diminishing the pain response to another simultaneously occurring stimulus at a distant location[95-97]. However, the stimuli do not have to be simultaneous. One painful stimulus may in fact have a hypo- or analgesic effect in relation to another subsequent painful stimulus. The widely recommended term for this is "conditioned pain modulation"[98, 99], and it has been utilized in studies involving adolescents with chronic pain conditions[100] and in children experiencing functional abdominal-pain disorders[101]. In these contexts, the intensity of pain from a test stimulus is measured both before and after the application of a conditioning painful stimulus.

Another form of endogenous pain modulation is exercise-induced hypoalgesia, which is characterized by a reduction in pain following single episodes of exercise, particularly in healthy individuals[102]. This effect is evidenced by increased pain thresholds and tolerances as well as reduced pain perception during and after physical activity. However, while exercise-induced hypoalgesia is a consistent finding in healthy populations[102], the pain-modulating effects of exercise are less predictable in individuals with musculoskeletal pain[102], who may experience either unchanged or heightened pain sensitivity following physical activity if their endogenous pain modulation is deficient[103].

Prolonged or repeated harmful stimulation, particularly due to sustained or intense activity of dorsal-horn neurons, may lead to a more widespread hyperexcitability of central nociceptive pathways, resulting in generalized hyperalgesia[92]. Generalized hyperalgesia — measured by means of local and remote pressure-pain thresholds — has been shown to exist in adolescents with HSD/hEDS[82]. However, endogenous pain modulation and exercise-

induced hypoalgesia have never been investigated in this population. Hence there is a clear need to do so.

Consequences of HSD/hEDS

Adolescents with HSD/hEDS encounter functional problems. They can exhibit limited physical capacity[104], joint problems (often affecting the ankle and knee), and delayed motor development[105, 106] as well as an increased risk of joint dislocation, especially in the shoulders and patella[35, 52]. Adolescents with HSD/hEDS self-report a lower health-related quality of life (HRQOL) than their healthy peers[107-110]. Moreover, low HRQOL scores were found to be associated with pain[107, 109] and fatigue[108-110] in these adolescents. Further, adolescents with HSD/hEDS may encounter problems in everyday life because of their disabilities, in contexts such as physical-education classes in school and leisure activities such as running[111, 112], exerting a negative impact on their social function[106]. A questionnaire study found that pain, fatigue, and fear of injury were barriers to exercise in adults with HSD/hEDS[113]. Families of adolescents diagnosed with HSD/hEDS primarily seek care for pain and for the limitations resulting from the adolescents' inability to move and participate in activities as they would like to. On a similar note, adolescents with chronic pain in the general population often avoid activity because they are afraid that it might worsen their pain[114]. Over time, this leads to a reduced ability to function, a lower quality of life[114], and a low level of attendance in school[115, 116]. These individuals tend to grow into adults with an increased vulnerability to pain[117]. Considering the above, the primary focus of clinical management for adolescents with HSD/hEDS is to improve their ability to function. However, a meta-analysis showed limited evidence regarding the impact of physical and psychological treatment modalities on improving function in adolescents with HSD/hEDS[10]. It is important to understand more about hypermobility in order to be able to help these adolescents properly. For this reason, the focus of this thesis is on understanding the impact that HSD/hEDS has on pain, fatigue, and physical activity.

HSD/hEDS and fatigue

Alongside pain, fatigue is a cardinal symptom in adolescents with HSD/hEDS[118, 119]. It is associated with fear of movement, anxiety, sleep disturbance, and poor health-related quality of life[2, 118]. Fatigue in itself is a multifaceted problem, characterized by patients with HSD/hEDS as an even more disabling symptom than pain. It can be defined as "an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion, which is not the same as muscle weakness"[2].

Sommer et al.[120] showed that fatigue occurs in about 20 percent of the community-based pediatric population and that it is generally more frequent in girls than in boys. In a study of pediatric patients aged 14–18 years with varying heritable connective-tissue disorders, findings did not indicate that the entire group had a high incidence of fatigue[121]. However, one subgroup consisting of pediatric patients diagnosed with hEDS (27 percent of the study population) had a significantly higher incidence of severe fatigue compared both with normative data and with other subgroups in the study. The hEDS subgroup also reported higher degrees of pain, disability, and general health issues compared with normative data[121].

Research has shown that fatigue significantly impacts health outcomes in a population-based cohort, independently of chronic pain[122]. To this should be added that chronic pain is more common in individuals with fatigue in this population. Furthermore, improvement of fatigue was correlated with improvement in health-related external measures as well as improvement in pain[122].

Voermans et al.[104] showed that both pain and fatigue have a large impact on individuals with hEDS. What is more, in adolescents with mild to moderate physical disabilities, fatigue has been associated with lower physical activity, making this an important area to study further[123].

HSD/hEDS and physical activity

Physical activity, defined as any bodily movement that increases energy expenditure beyond resting levels[4], encompasses a broad spectrum of activities, including play, games, sports, transportation, recreation, physical exercise, and planned workouts. Physical activity ranges from sedentary behavior (e.g., watching television) over light-intensity physical activity (e.g., doing the dishes) to moderate-to-vigorous physical activity (e.g., brisk walking or running)[124]. Such activity is often integrated into various contexts, such as family gatherings, school events, or community engagements. Engaging in physical activity offers numerous benefits beyond just physical fitness. For example, it also contributes to mental and emotional well-being[11] and to social participation.

The recommended total daily accumulated amount of physical activity for children and adolescents aged 5–17 years is at least 60 minutes at moderate to vigorous intensity[18]. Engaging in physical activity beyond 60 minutes per day yields additional health benefits. The majority of daily physical activity should be aerobic, but anaerobic vigorous-intensity activities that strengthen muscles and bones should be included at least three times per week[18].

One of the United Nations' major global-development goals is to promote health worldwide by promoting physical activity[11]. Studies have shown that regular physical activity has positive effects on both physical and mental health[125]. It can help reduce stress, anxiety, and depression as well as improving self-esteem and self-confidence in adolescents[126]. Many forms of physical activity, such as team sports or group exercise, promote social interaction and participation.

In summary, adolescents with HSD/hEDS face unique challenges that can affect their participation in physical activities, both in school settings and during leisure time. Because of their disabilities and limited physical capacity, their lower levels of activity may be lower than those of their peers[105]. While existing research highlights these concerns[105], there is a need for further studies utilizing objective measurement methods to gain a deeper understanding of those adolescents' experiences.

Physiotherapy management

Physiotherapy management in adolescents with HSD/hEDS

Physiotherapy is an important part of the multiprofessional care aimed at improving well-being and quality of life in adolescents with HSD/hEDS[36, 127]. At present, there is no universal consensus regarding recommended treatment interventions for these adolescents. In Sweden, as well as internationally, there is a lack of guidelines with evidence-based information about the effectiveness of various interventions[127]. This lack of information about the effectiveness — and appropriate dosing — of physiotherapy interventions obviously makes it difficult for therapists to know what interventions would be the most appropriate in order to ameliorate a given patient's symptoms and improve his or her daily function[128].

A large survey of 946 adults with HSD/hEDS aged 18–40 years investigated factors influencing exercise behavior, exercise preferences, barriers to exercise, and participants' experiences of physiotherapy[129]. Participants who agreed with statements to the effect that exercise was beneficial for the long-term management of their condition, helped them control their pain, and was good for their overall well-being were likely to exercise more than participants who strongly disagreed with those statements. Further, the likelihood of participants reporting high volumes of exercise was greater if they had received exercise advice from a physiotherapist. The most-cited barriers to exercise were fatigue and fear of injury. The forms of exercise reported as most helpful were swimming, walking, and Pilates[129].

There is limited research exploring physiotherapy interventions for adolescents with HSD/hEDS. The existing literature consists primarily of case reports and case series[130-132] as well as a few before–after studies without control groups[133-136]. However, two randomized controlled trials (RCTs) have been conducted in children and adolescents[137, 138]. These studies, led by Pacey and Kemp, respectively, are the only RCTs specifically examining exercise programs for the population in question, and they offer more rigorous evidence of the effects of exercise-based interventions.

Kemp et al.[137] studied 57 children and adolescents aged 7–16 years over a six-week intervention, with follow-ups two and three months post-

intervention. The researchers compared a targeted exercise program focused on functional stability and joint control with a general exercise regimen aimed at enhancing muscle strength and overall fitness. Both groups reported reductions in pain[137].

Pacey et al.[138] evaluated 29 children and adolescents aged 7–16 years with HSD/hEDS, comparing the outcomes of a strength and joint-control program using neutral knee extension versus the full range of hypermobility over an eight-week period. Besides examining stability and knee pain, the study also assessed the impact on the patients' global impression of change, functional abilities, and quality of life. The findings indicated that an individualized and progressive exercise program not only reduced knee pain but also improved muscle strength and psychosocial health[138].

In another study, To et al.[139] investigated the effects of a 16-week strength-training program, comparing patients with HSD and a control group. Their results revealed that, while the participants with HSD started at a lower baseline of muscle strength, they improved at a similar rate to their healthy counterparts[139].

Birt et al.[140] explored factors that influence the success of rehabilitation programs in children with joint hypermobility. Their findings highlighted the critical role of family involvement, with adherence to physical-activity prescriptions being strongly linked to parental motivation and the ability to incorporate exercise into daily family routines. Conversely, non-compliance was associated with factors such as low parental supervision, a lack of understanding of the importance of the treatment prescribed, and time constraints[140]. These findings can be used to improve adherence to prescriptions concerning exercise in the home environment.

Additionally, studies have demonstrated that enjoyable and engaging physical activities can have a positive impact on pain levels and motivate children to participate in regular physical activity, which is vital for managing symptoms[141].

Theoretical framework

Theoretical framework

In physiotherapy, theoretical frameworks in general are essential for systematically understanding and applying treatment methods[142, 143]. Frameworks provide a structured understanding of physiological and biomechanical processes and of the impact that those processes exert on function and movement. By employing theoretical frameworks, physiotherapists can develop evidence-based treatment plans and enhance patient care by integrating theories with practical application[142].

Theoretical frameworks are also fundamental in physiotherapy research, because they guide the design and interpretation of studies to ensure that the research will be grounded in established theories and will contribute to the development of effective, evidence-based practices[142].

This thesis incorporates two theoretical frameworks — the Biopsychosocial Model and the Fear-Avoidance Model — along with the International Classification of Functioning, Disability, and Health (ICF). These are described in more detail below.

The Biopsychosocial Model

Health and illness often need to be understood not just from one perspective, but rather as interconnected biological, psychological, and social phenomena.

The Biopsychosocial Model is a comprehensive explanatory framework in medicine and health that considers the interaction between biological, psychological, and social factors to understand health, illness, and care. It was introduced by the American psychiatrist George Engel in 1977[80]. He argued that the biomedical view of disease must be replaced with a model that assigns equal value to the psychological and social aspects of health as it does to the biological aspect of it. In his opinion, these three perspectives interact and influence disease onset, and they must all be considered in the investigation and treatment of illnesses[80].

Biological factors encompass the body's physiological processes, genetics, and any biochemical causes of disease[144]. Psychological factors include an individual's thoughts, feelings, and behaviors as well as his or her perception and management of illness[144]. Social factors embrace an individual's societal circumstances, such as family, culture, socioeconomic status, work, and social support, all of which can affect health and well-being.

The biopsychosocial perspective emphasizes the importance of treating not only the symptoms of a disease but also its underlying causes and the factors influencing an individual's ability to cope with illness and recover from it[80]. It is used in medicine, psychology, and other healthcare professions to develop more holistic and patient-centered care strategies.

Fear-Avoidance Model

Cognitive-emotional factors such as fear of pain and pain catastrophizing significantly contribute to the process of central sensitization[145]. Fear of pain and pain catastrophizing are factors associated with increased pain and disability in both children and adults[146, 147]. Fear avoidance refers to a fear of pain, injury, or worsening of a condition that makes a person avoid certain activities. The best-known and most-applied fear-avoidance model is the cognitive model of fear avoidance presented by Vlaeyen et al.[148].

The fear-avoidance model by Vlaeyen et al.[149] explains how patients with pain develop and maintain chronic pain through psychological processes. Initially, an individual experiences pain owing to injury or stress. According to the model, this acute pain can lead to two possible responses[150]:

1. **Adaptive response**: If the pain is perceived as non-threatening, the individual continues normal activities. This eventually leads to recovery.
2. **Maladaptive response**: If the pain is perceived as threatening, it can induce fear and anxiety. This leads to a cycle of avoidance behavior.

In the maladaptive response, fear of pain (pain catastrophizing) leads to hypervigilance and avoidance of activities that might cause pain, resulting in physical deconditioning, disability, and increased pain perception. This avoidance reinforces fear, creating a vicious circle where the individual becomes increasingly disabled and the pain persists or even worsens[149, 150] (Figure 3).

This model highlights the role of psychological factors such as fear, anxiety, and catastrophizing during the transition from acute to chronic pain.

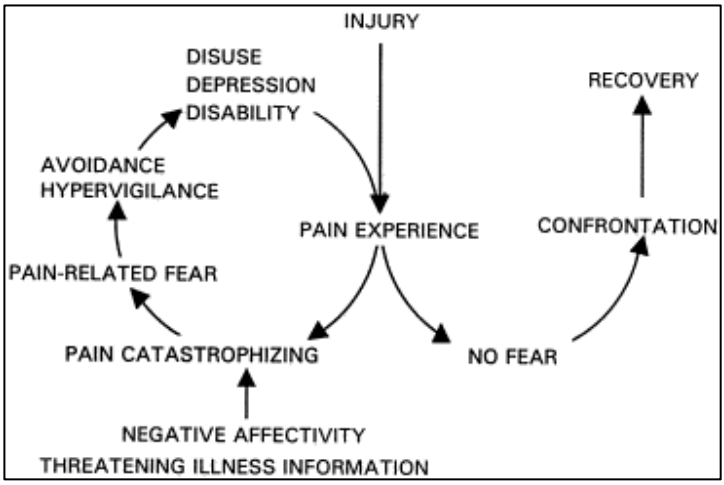


Figure 3. Fear-Avoidance Model, from Vlaeyen and Linton (2012)[149].
Reproduced with permission.

Asmundson et al.[151] discuss the Fear-Avoidance Model in relation to chronic pain and highlight the role of parents in influencing children's pain experiences, particularly from a fear-avoidance perspective. According to the research presented, parents' own fear-avoidance behaviors and beliefs can significantly shape their children's responses to pain. When parents exhibit fear of pain or anxiety about it, they may reinforce avoidance behaviors in their children, inadvertently encouraging the children to avoid activities that might cause pain, which can contribute to the development of chronic-pain issues[151].

International Classification of Functioning, Disability, and Health

The International Classification of Functioning, Disability, and Health (ICF)[152] offers an overarching framework for measuring health and disability that can help to describe the complexity of HSD/hEDS[153].

The ICF provides a comprehensive picture of an individual's health, divided into domains. There is also a child and youth version of it: the ICF-CY[152, 154]. A person's health is determined by an interaction between diagnosis, functioning, and disability[155]. The ICF has been designed to provide a single, standardized language and structure for describing health and health-related conditions and their consequences. It provides a scientific basis for understanding and studying health and health-related states[155].

The various ICF domains describe physical, personal, and social perspectives on an individual. Functions are divided into three domains. The first one is **Body Functions and Structures/Impairments**, where *body functions* relate to the physiological functions of body systems, including psychological functions, and *body structures* relate to anatomical parts of the body such as organs, limbs, and their components. The second domain is **Activity/Activity Limitations**, which refers to a person carrying out a task or action, including walking, standing up, or cycling. The third one is **Participation/Restrictions**, which refers to a person's involvement in a life situation, including school attendance, socializing with friends, or everyday activities. In addition, the ICF also lists **Personal Factors**: a particular background to an individual's life and living, including past and current experience, overall behavior patterns, and character; and **Environmental Factors**: the physical, social, and attitudinal environment in which people live and work — both of which interact with all of the aforementioned concepts[155].

Van der Poeg et al.[156] modified the original ICF model to incorporate physical activity. In physiotherapy, the ICF can help to provide a holistic picture of a patient's difficulties, which can be used as support in developing an individual treatment plan[128] (Figure 4).

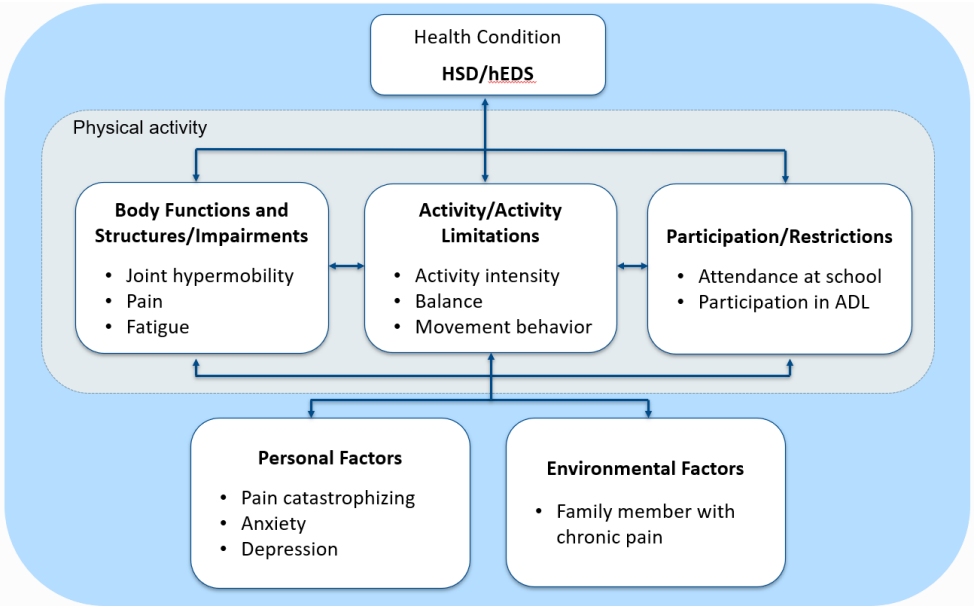


Figure 4. A schematic view of the structure of the International Classification of Functioning, Disability, and Health (ICF), modified to include physical activity and applied to our research.

ADL = activities of daily living.

Rationale

Rationale

Previous research has demonstrated that adolescents with HSD/hEDS experience significant impacts on their daily lives. Although research has advanced, it has not yet identified the underlying factors that may help explain why some adolescents with hypermobility suffer severe symptoms while others remain relatively unaffected.

Participation in school and recreational activities is important for the development and well-being of adolescents. Physical exercise has been shown to have a pain-relieving effect and can reduce functional impairments in adolescents with HSD/hEDS. However, there are currently no treatment strategies that provide long-term benefits or effectively support adolescents in completing their education, pursuing further studies, and leading active adult lives.

Central sensitization has been put forward as a possible explanation for the occurrence of generalized pain in adolescents with HSD/hEDS, and it may also affect perceived fatigue and levels of physical activity.

In this context, several specific knowledge gaps have been identified and need to be addressed. First, we have a limited understanding of how hypermobility affects physical performance, such as balance and participation in activities of daily living. Second, there is a need for a deeper comprehension of the underlying pain mechanisms in these adolescents. Third, there is a lack of knowledge regarding how pain influences their levels of physical activity. And fourth, the impact of fatigue on physical activity and participation in activities of daily living among these adolescents remains largely unexplored.

By attempting to address these gaps, this thesis aims to provide a more comprehensive understanding of the challenges faced by adolescents with HSD/hEDS.

Aim

Aim

The overall aim of this thesis is to better understand pain and its impact on functioning in adolescents with HSD/hEDS.

The research project presented in this thesis consists of four studies, each reported in one paper but all addressing interconnected, specific research questions that collectively contribute to the overall aim as stated above.

Specific aims of the four studies:

The aim of Study I was to describe hypermobility, balance, pain, activity, and participation in children with HSD/hEDS and compare these characteristics with those of a control group.

The aim of Study II was to investigate the feasibility of a study protocol intended to investigate the presence of signs of central sensitization through endogenous pain modulation and exercise-induced hyperalgesia in adolescents with HSD/hEDS compared with a healthy control group.

The aim of Study III was to explore signs of central sensitization, including exercise-induced hyperalgesia, and to examine fatigue severity in adolescents with HSD/hEDS compared with a healthy control group.

The aim of Study IV was to investigate daytime and nighttime movement behavior, using accelerometers, in adolescents with HSD/hEDS compared with a healthy control group, as well as to investigate the association between fatigue and daytime and nighttime movement behavior, with pain catastrophizing as a confounder.

The research hypotheses for this thesis are presented in Table 3.

Table 3. Research Hypotheses

Study I	• Adolescents presenting with HSD/hEDS experience more pain than a healthy control group. • Adolescents presenting with HSD/hEDS are less active than a healthy control group. • Adolescents presenting with HSD/hEDS have lower balance scores, as tested with the Bruininks–Oseretsky Test of Motor Proficiency (BOT-2), than a healthy control group.
Study II	• The planned study protocol is feasible. • The recruitment process for adolescents with HSD/hEDS and a healthy control group is effective. • Central sensitization can be investigated using pressure-pain thresholds and endogenous pain modulation in adolescents with HSD/hEDS compared with a healthy control group.
Study III	• Adolescents presenting with HSD/hEDS respond with impaired exercise-induced hypoalgesia after exercise as compared with a healthy control group. • Adolescents presenting with HSD/hEDS and with signs of inefficacy in endogenous pain modulation score higher on the PedsQL™ Multidimensional Fatigue Scale than a healthy control group.
Study IV	• Adolescents presenting with HSD/hEDS spend more time in sedentary behavior than a healthy control group. • Adolescents presenting with HSD/hEDS spend less time in moderate to vigorous physical activity than a healthy control group. • Perceived fatigue is an explanatory factor for spending less time in moderate to vigorous physical activity and more time in sedentary behavior. • Nighttime restlessness in sedentary behavior is an explanatory factor for perceived fatigue.

Participants and methods

Participants and methods

This thesis encompasses several different study designs and participant groups (Table 4). Study I was a comparative cross-sectional case-control study. Study II was designed to determine the feasibility of a prospective experimental case-control study. Study III was a prospective, experimental case-control study. Finally, Study IV was a prospective, exploratory case-control study. In all studies, adolescents with HSD/hEDS were compared with a healthy control group.

Participant selection

A total of three different groups of participants were recruited, with Studies III and IV using the same group. The adolescents in the patient and control groups and their guardians received study information through letters and were invited to participate. Potential participants in the control group were informed that they had to be healthy and free of pain. Spoken information was offered to all participants and guardians. Participants under 15 years provided verbal assent, and those over 15 years as well as all guardians provided written consent, before they came to their assigned clinic appointment.

HSD/hEDS groups

Participants in Studies I–IV were identified through the electronic medical records at the Queen Silvia Children's Hospital in Gothenburg, Sweden [C]. For Studies III and IV, recruitment was expanded to include participants not only from the Queen Silvia Children's Hospital but also from the children's primary healthcare clinics in the healthcare districts of Gothenburg and South Bohuslän and, from the Skaraborg Hospital, all located in Sweden, as well as from the local patient organization.

[C] The ICD-10 search terms "Q796" and "M357" were used for all studies.

Table 4. Overview of the research design of the different studies

	STUDY I	STUDY II	STUDY III	STUDY IV
Design	Cross-sectional	Feasibility	Experimental case control	Exploratory case control
Age, years	8–16	13–17		
Study sample total, n	44	19	84◊	82◊
Study sample HSD/hEDS group, n	20	10	37	37
Female/male, n	8/12	6/4	27/10	27/10
Study sample control group, n	24	9	47	45
Female/male, n	11/13	5/6	34/13	34/11
Recruitment HSD/hEDS	Queen Silvia Children's Hospital/SU		Queen Silvia Children's Hospital /SU, children's primary healthcare clinics in the healthcare districts of Gothenburg and South Bohuslän, Skaraborg Hospital, patient organization	
Recruitment control group	Schools, friends, colleagues		Facebook, hospital staff, friends, colleagues	
Enrolment hospital	Queen Silvia Children's Hospital/SU		Queen Silvia Children's Hospital/SU, primary healthcare rehabilitation reception, Skövde	
Enrolment period	February 2009–April 2009	November 2019–April 2020	November 2022–August 2023	
Methods	DMS, BOT-S, PROM, DM	BS, PPT, CMP, EIH, NRS, BORG, HR, DM, PROM	BS, PPT, EIH, NRS, PROM, NRS, BORG, HR, DM	BS, Accelerometer, PROM, DM
Outcome assessments	One assessment	Baseline, after intervention		Over 7 days

SU = Sahlgrenska University Hospital; DMS = Del Mar Scale; BS = Beighton Scale; PPT = pressure-pain thresholds; CMP = conditioned pain modulation; EIH = exercise-induced hypoalgesia; BORG = Borg Rating of Perceived Exertion Scale; HR = heart rate; NRS = numerical rating scale; DM = demographic measures; PROM = patient-reported outcome measures; ◊ Same study population.

Control groups

Participants for the control group of healthy adolescents, without a history of medical problems or regular use of medications, were recruited for Study I through schools in the region. Additional participants for Study I were recruited via convenience sampling through friends and colleagues, while Study II participants were also recruited using this method. A third control group was recruited for Studies III and IV through hospital staff and advertisements on social media. Participants in all three control groups were matched for sex and age as closely as possible with the participants in the respective HSD/hEDS group.

The participants were compensated for their participation with a cinema ticket financed through project funding.

Study I

Participants

Recruitment for this study was carried out between February 2009 and April 2009. A total of 44 adolescents were included, 20 adolescents with HSD/hEDS and 24 healthy adolescents. Inclusion criteria were age 8 to 16 years and a diagnosis of HSD or hEDS. Exclusion criteria were all other known disorders. For the control group, inclusion criteria were age 8 to 16 years and no history of medical problems or regular use of medications.

Study procedures

The adolescents completed an activity diary and a pain diary linked to a pain-location drawing (see section “Assessment of pain”), with parental assistance if necessary, before handing them in when they came for assessment. They underwent a medical examination for HSD/hEDS performed by an independent physician in accordance with the Brighton Criteria and Villefranche Criteria[32, 48]. This examination ensured that the selected patients met the criteria and confirmed that the control-group participants did not. Further, an independent physiotherapist evaluated all participants. They were assessed with regard to hypermobility and balance during a single visit to the Department of Physiotherapy at the Queen Silvia Children’s Hospital. The participants did not perform any stretching or warm-up exercises prior to the tests. Finally, the Frequency of Participation Questionnaire was

completed by the adolescents, with parental assistance if necessary, at the time of the assessment.

Study II

No power calculation was performed for this feasibility study.

Participants

Recruitment for this study was carried out between November 2019 and April 2020. A total of 19 adolescents were included, 10 adolescents with HSD/hEDS and 9 healthy adolescents. Inclusion criteria for the patient group were adolescents aged 13 to 17 years, diagnosed with HSD or hEDS. Inclusion criteria for the control group were adolescents aged 13 to 17 years without a history of medical problems or regular use of medications. Exclusion criteria common to both groups were as follows: (1) unable to read or understand Swedish, (2) pregnant or within one year postpartum, and (3) diagnosed with a (comorbid) neurological, rheumatic, musculoskeletal, or metabolic disorder. In addition, participants were excluded from the patient group if they had other syndromes including hypermobility, such as Marfan Syndrome, Osteogenesis Imperfecta, or other types of EDS. Participants in the control group were excluded if they had experienced pain that had persisted for more than 24 hours during the three months prior to their examination. In addition, the participants in the control group needed to have an overall less active lifestyle. For this reason, participants were excluded if they exercised more than three times per week. A preliminary review of the patients' medical records was conducted to confirm their diagnosis and to ensure that they fulfilled the inclusion criteria.

Study procedures

All participants visited the hospital on two occasions, seven days apart. During the first visit, participants underwent a medical examination by an independent physician in accordance with the 2017 criteria for HSD/hEDS[157]. This examination ensured that the selected patients met the 2017 criteria and confirmed that the control-group participants did not. Following this, an independent physiotherapist asked all participants to complete a self-report questionnaire.

Participants were instructed to abstain from physical exercise for at least 48 hours before the second visit and to avoid consuming caffeine, alcohol, and nicotine on the day of that visit. For ethical reasons, patients were permitted to take non-opioid pain medication as outlined in the first step of the World Health Organization analgesic ladder (COX inhibitors and paracetamol). However, they were asked to refrain from taking these medications for 24 hours before their second visit.

During the second visit, various pain measurements were performed. An independent physiotherapist explained the measurement procedures to the participants. Instrument-placement points were measured and marked on their skin with a pen. Measurements of pressure-pain thresholds were performed three times at each point. After a 10-minute break during which participants washed their hands and were offered juice, they placed their non-dominant hand in cold water for the test of conditioned pain modulation, and PPT measurements on the trapezius muscle were repeated. Self-reported and experimental pain measurements were recorded both during and immediately after the hand was removed from the water. Following a 15-minute break, participants performed a submaximal workout on a bicycle ergometer. Self-reported and experimental pain measurements, as well as self-estimated exhaustion, were recorded immediately after they completed the exercise.

Studies III and IV

A priori power analysis was performed, using G*Power 3.1.9.2., for sample-size estimation with an alpha of 0.05 and strength of 0.80. The analysis was based on data from Study II using the mean PPT value at the tibialis-anterior muscle. This yielded a target total number of participants of 80 — 40 per group. No separate power analysis was performed for activity measurement.

Participants

Recruitment for these studies was carried out between November 2022 and August 2023. A total of 84 adolescents, 37 adolescents with HSD/hEDS and 47 healthy adolescents, participated in Study III. Study IV included a total of 82 adolescents, 37 adolescents with HSD/hEDS and 45 healthy adolescents. The

participants were recruited in the healthcare districts of Gothenburg, South Bohuslän, and Skaraborg. The inclusion and exclusion criteria were the same as in Study II except that, in contrast to Study II, participants in the control group were not allowed to have engaged in elite-level sports, although they were allowed to lead an active life in other respects. A preliminary review of patients' medical records was conducted to confirm their diagnosis and to ensure that they fulfilled the inclusion criteria.

Study procedures

A single assessment session was conducted for Studies III and IV together. Participants were given a choice between two standardized assessment locations, Gothenburg and Skövde, equipped with identical apparatus. They were instructed to refrain from moderate to vigorous physical exercise for 48 hours prior to the measurements and to avoid consuming caffeine, alcohol, and nicotine on the day of measurement. While non-opioid pain medication (COX inhibitors, paracetamol) was permitted for patients on ethical grounds, all participants were asked to abstain from analgesics for at least 24 hours before the measurements.

On the day of the assessment, demographic data and pain scores were collected by a physiotherapist (the author of this thesis). This was followed by a medical examination by an independent physician in accordance with the 2017 HSD/hEDS diagnostic criteria[157]. An independent physiotherapist provided instructions on the measurement procedures, marked the points for the tests of pressure-pain thresholds, and carried out the measurements, which were repeated three times at each site. Subsequently, participants performed a cycling test. Data about self-reported pain, exhaustion, and experimental pain measures were collected immediately post-exercise. Finally, participants completed questionnaires. The independent physician and the independent physiotherapist were both blinded to the participants' group affiliation. To ensure completeness of data, the questionnaires were checked immediately upon submission, allowing any missing information to be collected on the spot.

Measurements

An overview of the measurement methods used for data collection in Studies I–IV is presented in Table 5.

Table 5. Overview of the measurement methods used for data collection in Studies I–IV

	Study I	**Study II**	**Study III**	**Study IV**
Sociodemographic	Q	Q	Q	Q
Joint hypermobility	Del Mar Scale	Beighton Scale	Beighton Scale	Beighton Scale
Physical activity	Diary	-	-	Accelerometer + supplementary diary
Balance	BOT-2 balance	-	-	-
Pain measurements				
Pain intensity	NRS	NRS	NRS	NRS
Pain location	PD	Q	PD	PD
Pain duration	Q	Q	Q	Q
Measurements of central sensitization	-	PPT; CMP; EIH	PPT, EIH	-
Limitation of pain	Diary	-	-	-
Patient-reported outcome measures				
Participation	FoP	-	-	-
Fatigue	-	PedQL-F	PedQL-F	PedQL-F
Pain catastrophizing	-	PCS-C	PCS-C	PCS-C
Anxiety and depression	-	HADS	HADS	-

BOT-2 balance = Bruininks–Oseretsky Test of Motor Proficiency; CMP = conditioned pain modulation; EIH = exercise-induced hypoalgesia; FoP = Frequency of Participation Questionnaire; HADS = Hospital Anxiety and Depression Scale; PCS-C = Pain Catastrophizing Scale — Child version; PD = pain drawing; PedQL-F = Pediatric Quality of Life Multidimensional Fatigue Scale; PPT = pressure-pain thresholds; Q = self-developed questionnaire.

Sociodemographic information and other relevant background variables for the different studies were collected using a self-developed questionnaire for both adolescents and guardians.

Assessment of joint hypermobility

To assess hypermobility in Study I, the Hospital Del Mar criteria for hypermobility (the Del Mar Scale) was used. The assessment was conducted by an experienced physiotherapist using the standardized protocol pertaining to the measurement scale[40]. Concretely, hypermobility was measured with a goniometer. If hyperextension of the knee joint was required, a roll was placed under the ankle so that the passive range of motion could be measured. The Del Mar Scale evaluates joint hypermobility in ten joint pairs and in spinal flexion (Table 6). One point is awarded for each item, independently of whether only one side or both sides are rated as hypermobile. Hence a maximum of eleven points can be attained. The Del Mar Scale has demonstrated good reliability in adults, for whom the cutoff for hypermobility is 4/11[40]. However, no cutoff values are available for adolescents. Of the eleven items, five are derived from the Beighton Scale. The Del Mar Scale has not been tested for its measurement properties in adolescents.

In Studies II–IV, hypermobility was assessed using the Beighton Scale[39, 158]. The assessment was performed by an experienced orthopedic physician using a standardized protocol. Hypermobility was measured with a goniometer. If hyperextension of the knee joint was required, a roll was placed under the ankle so that the passive range of motion could be measured. The Beighton Scale evaluates the ability to (1) passively dorsiflex the fifth metacarpophalangeal joint to > 90 degrees; (2) oppose the thumb to the volar aspect of the ipsilateral forearm; (3) hyperextend the elbow to > 10 degrees; (4) hyperextend the knee to > 10 degrees; and (5) place the hands flat on the floor without bending the knees (Figure 5). A maximum of nine points can be attained, with one point awarded for each side of the body for items 1–4 and one point awarded for item 5. Different cutoff values are recommended for

different age groups when the Beighton Scale is used as a criterion for hEDS[3, 39] (Table 7). Here, generalized hypermobility was defined, for all participants, as scoring six or higher on the Beighton Scale.

Table 6. Protocol for the Del Mar Scale

Body part	Description	Physical placement
Shoulder joint	Passive lateral rotation > 85 degrees	Standing
Elbow joint*	Passive hyperextension of the elbow to > 10 degrees	Standing
Thumb*	Oppose the thumb to the volar aspect of the ipsilateral forearm	Standing
Fifth finger*	Passive dorsiflexion of the fifth metacarpophalangeal joint to > 90 degrees	Standing, elbow joint 90-degree flexion, palm against examination bench
Hip	Hip abduction to > 85 degrees	Supine, knee joint straight
Knee-joint extension*	Hyperextension of the knee to > 10 degrees	Supine, knee joint straight
Knee-joint flexion	Hyperflexion of the knee to > 90 degrees	Supine, knee joint straight
Patella	Passive medial/lateral movement to and above midline	Supine, knee joint straight
Ankle	Dorsal flexion of the ankle to > 30 degrees	Supine, knee joint straight
First toe	Passive extension of the first metatarsophalangeal joint to > 90 degrees	Supine, knee joint about 90-degree flexion, ankle 90-degree flexion
Spinal flexion*	Placing both hands flat on the floor without bending the knees	Standing

* Item included in the Beighton Scale.

Table 7. Presence of generalized hypermobility, assessed in accordance with the Beighton Scale[39]

Age range	Cut-off points
Children/adolescents pre-puberty	Beighton Scale ≥ 6 points
Adolescents from puberty until age 50 years	Beighton Scale ≥ 5 points
(≤ 50 years with an injury affecting Beighton)	*Beighton Scale ≥ 4 points AND 5-PQ ≥ 2 points*
Adults > 50 years	Beighton Scale ≥ 4 points
(>50 year with an injury affecting Beighton)	*Beighton scale ≥ 3 points AND 5-PQ ≥ 2 points*

5-PQ = the Five-Part Questionnaire on Hypermobility.

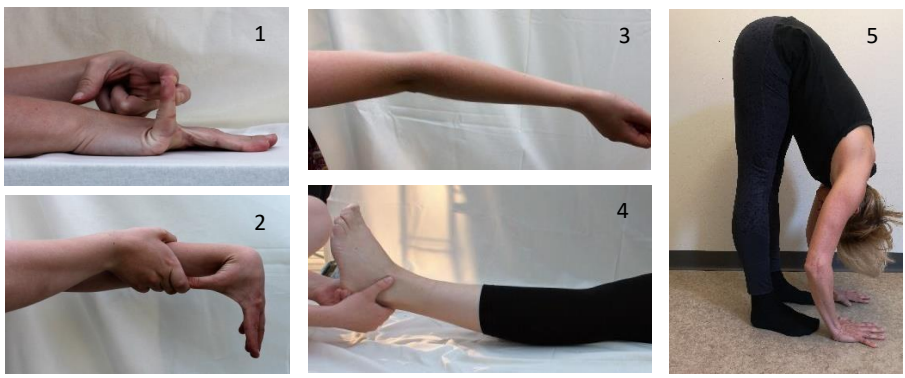


Figure 5. Beighton Scale.
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Assessment of pain

In Study I, pain intensity was measured by means of a pain diary. This instrument has demonstrated good validity for children with headaches[159]. Participants recorded the pain they felt in a diary four times a day for two weeks. Pain intensity was assessed using a five-step scale: 0 = “no pain”; 1 = “pain that I only notice if I pay attention”; 2 = “pain that I can occasionally

ignore"; 3 = "pain that makes it difficult to concentrate, allowing only easy activities"; 4 = "pain so severe that I cannot do anything." Additionally, the participants reported to what extent the pain limited their activity during the day.

In Studies II–III, mean pain intensity was measured using a 0–10 numerical rating scale (NRS)[160], with 0 = "no pain" and 10 = "the worst possible pain" as endpoints. This instrument, the NRS-11, is commonly used to assess pain intensity in pain research involving children and adolescents[160-162], and there is good evidence supporting its reliability and validity in individuals as young as six years of age[162, 163].

Pain localization was mapped using a pain drawing[164] which displayed full-body images from both the front and back, allowing participants to accurately indicate the locations of their pain (Figure 6). In Study I, participants marked areas on a body image to indicate the location and type of pain, such as burning or oppressive sensations, for two weeks prior to the examination. The markings were summarized into a list ranging from most-marked body part to least-marked body part. In Study III, participants marked pain locations in two independent pain drawings: one for the day of the investigation and the other for pain locations experienced over the past three months. This approach was utilized to assess the distribution of pain. Participants were instructed to mark areas where they experienced pain and to indicate the frequency of this pain as either "always," "sometimes," or "rarely."

As part of the evaluation of the pain drawing, the body image was systematically divided into quadrants: left–right side, upper–lower segment. Specific axial regions were also delineated: the cervical spine, chest, thoracic spine, lower back, and stomach[165, 166] (Figure 6). This detailed mapping enabled a comprehensive assessment of pain presence by counting the number of pain locations and identifying the quadrants and axial regions affected.

The occurrence of pain was rated as follows: 0 = "no pain"; 1 = "localized pain in in a maximum of 2 joint pairs, 1 joint pair and 1 axial region, or a maximum of 3 axial regions"; 2 = "increased pain in at least five locations in one or to two quadrants and/or axial regions"; and 3 = "widespread pain in at least five

locations in three or more quadrants and/or axial regions”[166]. It is important to note that only pain reported as occurring “always” or “sometimes” was considered in this assessment. The purpose of this was to ensure a focus on pain experiences of a more chronic nature.

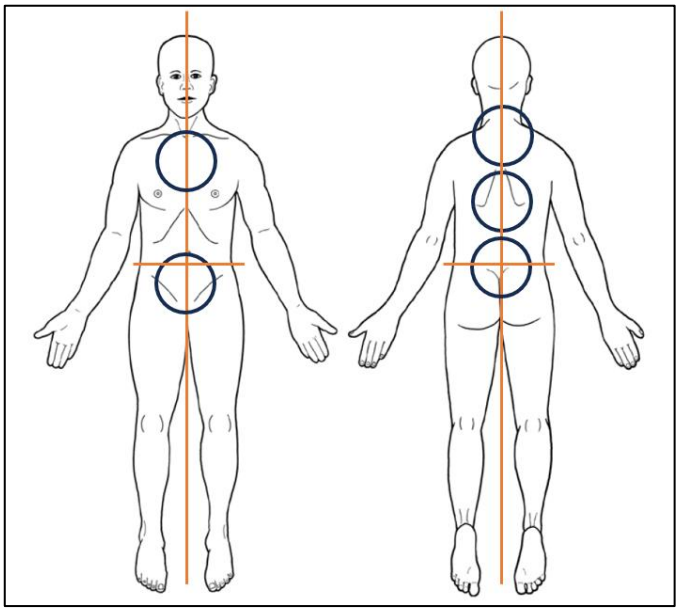


Figure 6. Pain Drawing.
The pain drawing is divided by orange lines into quadrants, with circles indicating axial regions.

Measurement of central sensitization

The assessment methods described below have not previously been tested in adolescents with HSD/hEDS. To obtain information about feasibility, the measurement methods for primary and secondary hyperalgesia, endogenous pain modulation, and exercise-induced hypoalgesia, as described below (Table 8), were tested in Study II and found to be feasible. In Study III, primary and secondary hyperalgesia as well as exercise-induced hypoalgesia were assessed.

Table 8. Measurements of central sensitization

Measurements of central sensitization **Defined as "an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity"[1].**		
Primary and secondary hyperalgesia	Endogenous pain modulation	Exercise-induced hypoalgesia
Measured by: Pressure-pain thresholds.	Measured by: Pressure-pain thresholds together with another conditioning stimulus (= conditioned pain modulation paradigm).	Measured by: Pressure-pain thresholds before and after exercise.
Clinical sign: Increased sensitivity to pain as compared with a healthy control group.	Clinical sign when deficient: Absence of the analgesic effect in response to the conditioning stimulus.	Clinical sign when deficient: Unchanged or increased sensitivity to pain after physical activity.

Primary and secondary hyperalgesia

Primary and secondary hyperalgesia was assessed by evaluating pressure-pain thresholds (PPTs) at a symptomatic test site (trapezius muscle) and three remote test sites (deltoid muscle [upper quadrants], tibialis-anterior muscle [lower quadrants], and paraspinal muscles of the lower back [axial]) using a hand-held pressure algometer (Wagner Instruments, FPX 25). The 1 cm^2 rubber tip of the algometer was positioned at an angle of 90 degrees in relation to the body part evaluated and pressure was applied at a rate of 1 kg/s (Figure 7).



Figure 7. Positioning of the algometer for measuring a pressure-pain threshold.

The participant was seated during the examination of the trapezius and deltoid test sites, lying down in a supine position for the examination of the PPTs in the lower back, and in a prone position for the examination of the PPTs in the tibialis anterior test sites. The participant was instructed to say "stop" as soon as the sensation of pressure changed into an uncomfortable feeling. At that point, the value shown on the display was noted. This procedure was repeated three times for each test site (with 30 seconds between measurements). The PPT measure recorded for a site was determined as the mean of the last two values; this has been found to be a reliable method in both children and adults[167]. The mean value for the trapezius muscle was used as a baseline for the measurements of conditioned pain modulation, and the mean values for the tibialis-anterior muscle and trapezius muscle were used as a baseline value for exercise-induced hypoalgesia, as described below.

The order of the PPT measurement points for primary and secondary hyperalgesia and exercise-induced hypoalgesia was randomized for each individual in both groups.

Endogenous pain modulation

Endogenous pain modulation was measured through conditioned pain modulation using a cold-pressure task as conditioning stimulus and mechanical stimulation to produce a test stimulus.

The conditioning stimulus involved participants placing their non-dominant hand in a cold pressor unit, with water maintained at a temperature of 12±1 °C[168]; to prevent localized warming around the hand, the water was kept in motion with a water circulator. The test stimulus involved a hand-held pressure algometer with a 1 cm^2 rubber tip and an application rate of 1 kg/s being used on the trapezius test site to measure PPT, exactly as described above in the section "Primary and secondary hyperalgesia."

To assess conditioned pain modulation, the test stimulus was first administered without the cold-water conditioning stimulus to establish a

baseline value. Then the cold-pressure condition was applied. The participant's non-dominant hand was immersed in cold water for one minute. During that time. The test stimulus was administered first after 20 seconds of immersion and then again after 50 seconds of immersion (that is, with 30 seconds between PPT measurements). Participants were instructed to leave their hand in the water throughout the process until they were told to take it out, which happened after a total of one minute of immersion. Immediately after removing their hand from the water, they were asked to rate the pain due to the immersion of the hand in cold water using the numerical rating scale (NRS) explained above.

The outcome measure for conditioned pain modulation was obtained by subtracting the PPT obtained during the baseline administration of the pressure stimuli (i.e., the mean of two PPT measurements) from the PPT obtained during the conditioning stimulus (which is also the mean of the two PPTs measured). Hence a positive change score represented an increase in the pain threshold, reflecting activation of pain-inhibitory mechanisms, while a negative change score represented a decrease in the pain threshold. A decrease or no change demonstrated a disturbed function of pain-inhibitory mechanisms.

Exercise-induced hypoalgesia

Exercise-induced hypoalgesia was measured by means of two PPT measurements, again using a hand-held pressure algometer with a 1 cm^2 rubber tip and an application rate of 1 kg/s, administered with 30 seconds between them at the trapezius muscle and the tibialis-anterior muscle immediately after the performance of an exercise test on a bicycle ergometer (Monark 828E). The participant began cycling with 0.5 kilopounds of resistance at a cadence of 50 revolutions per minute (equal to 25 Watts). The resistance then increased by 0.5 kilopounds after each minute[169]. To achieve effort but not exhaustion, cycling was interrupted either at 75 percent of the expected maximum heart rate (220 beats per minute minus the participant's age in years) or if the participant indicated that he or she experienced an effort corresponding to 15 on the Borg Rating of Perceived Exertion Scale (Borg RPE)[170]. Notes were made of values for maximal exercise capacity, such

as maximum resistance and peak heart rate during the cycling test. Self-estimated exhaustion was measured using the Borg RPE 6–20, with 6 = "no exertion," 15 = "hard/heavy exertion," and 20 = "maximum exertion"[170]. It was noted whether the participant interrupted the test because of fatigue in the legs or cardiovascular exhaustion.

To assess exercise-induced hypoalgesia, PPT measurements were first made before exercise to establish baseline values for each muscle. The change score was then calculated for each muscle separately. It was obtained by subtracting the baseline mean PPT value from the mean PPT value post-exercise. A positive change score represents pain inhibition or normal exercise-induced hypoalgesia, while a negative change score represents a decrease in pain threshold, reflecting pain facilitation or impaired exercise-induced hypoalgesia.

These assessment methods have not previously been tested in adolescents with HSD/hEDS. To obtain information about feasibility, the measurement methods for the conditioning stimulus had been tested in Study II and found to be feasible.

Measurement of balance

In Study I, the Bruininks–Oseretsky Test of Motor Proficiency (BOT-2)[171], which measures children's and adolescents' motor performance, was used to evaluate balance. The test was administered by an experienced physiotherapist. The balance subtest of BOT-2 consists of eight items: standing with feet apart on a line; walking forward on a line; standing on one leg on a line; standing with feet apart on a line with eyes closed; walking forward heel-to-toe on a line; standing on one leg on a line with eyes closed; standing on one leg on a balance beam; standing heel-to-toe on a balance beam; and standing on one leg on a balance beam with eyes closed. The stationary items are timed in seconds (up to a maximum of ten seconds), while the mobile ones are measured by the number of steps (up to a

maximum of six steps). The test has demonstrated good validity and reliability[171].

Measurement of physical activity

Activity diary

In Study I, an activity diary developed by the researchers was used. The participants documented their activities for two weeks, noting what they did and when. To evaluate the general impression of activity during those two weeks, three independent therapists — one occupational therapist and two physiotherapists — individually assessed the intensity of the recorded activities in each adolescent's diary. The overall level of physical activity was categorized as: 1 = "low" (only physically non-demanding activities such as walking short distances, playing in a sandpit, computer gaming); 2 = "moderate" (physical activity such as walking, swimming, or similar activities at least twice a week); or 3 = "high" (ball games, jogging, skiing, etc., at least twice a week). If the assessors disagreed about a participant's activity level, discussions were held afterward until agreement was reached. The activity diary has not been tested for validity or reliability.

In Study IV, a self-designed activity and sleep diary was used by the participants to record the times when they engaged in planned physical activities, the times when the accelerometer was removed, and the times when they went to bed and woke up.

Participation in activities of daily living

In Study I, participation in activities of daily living in school and during leisure time was measured using the Frequency of Participation Questionnaire (FPQ)[172]. The FPQ, which is designed to measure a child's or adolescent's participation across all areas of the International Classification of Functioning, Disability, and Health (ICF), consists of 14 questions regarding participation frequencies, each offering six response options for different frequency levels[172]. These questions pertain to the "life situations" domain of the ICF.

The FPQ has been translated into Swedish and is considered to have face validity. However, although the FPQ has been used in a major international study, data on its psychometric properties are not available[172].

The FPQ was supplemented with an open-ended question about the adolescent's need for rest: "How often do you need to rest?"

Physical activity — accelerometer

In Study IV, physical activity was measured with an Axivity AX3 triaxial accelerometer (Axivity Ltd, UK). In addition, a diary (as described above) was used for reporting sleep time. Data were collected at a rate of 50 Hz and within an acceleration range of ±8G (1G = 9.81 m/s^2). The size of the accelerometer is 23 x 32.5 x 7.6 mm, it weighs 11 g, and it is water resistant to a depth of 1.5 m for 1 hour. The AX3/AX6 OMGUI Configuration and Analysis Tool was used to program the accelerometers and to download and visualize data. The accelerometer was attached to the participant's right thigh with medical tape, 10 cm below the groin in the medial front thigh, for seven days. To reduce the risk of skin reactions, the edges of the accelerometer were rounded, and the accelerometer was padded. Additionally, adhesive for extra sensitive skin was used. In standing position, the accelerometer was orientated with the x-axis in the vertical direction, the y-axis in the horizontal medial-lateral direction and the z-axis in the horizontal anterior-posterior direction. Raw accelerometer data were processed to obtain a measure of movement intensity (milligravity, mg) in three-second epochs using the Frequency Extended Method. Movement intensity was then categorized into sedentary, light physical activity, moderate physical activity, vigorous physical activity, and very vigorous physical activity[173]. Time spent at an intensity of moderate or higher was merged into a measure called moderate-to-vigorous physical activity. All data were broken down into daytime and nighttime (sleep). A special sedentary variable was created for nighttime only, excluding sedentary with zero acceleration. This variable was named sleep movement.

Measurement of fatigue and cognitive-emotional factors

Fatigue

In Studies III and IV, fatigue was measured using the Pediatric Quality of Life Inventory — Multidimensional Fatigue Scale, Child Version (PedsQL-F)[174]. PedsQL-F is a self-report outcome measure, developed to assess fatigue in children and adolescents in different age groups, and it has been tested in various conditions[174-176]. The standard version of PedsQL-F was used with a one-month recall period[175]. It consists of 18 questions which are divided into three subscales containing six questions each: General Fatigue, Sleep/Rest Fatigue, and Cognitive Fatigue. The version for ages 13–18 years was used[177]. The response options are 0 = "never a problem"; 1 = "almost never a problem"; 2 = "sometimes a problem"; 3 = "often a problem"; and 4 = "almost always a problem," and responses are linearly converted to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0). Scale scores are calculated as the sum of the items divided by the number of questions answered, with higher scores indicating lower levels of fatigue and lower scores indicating higher levels of fatigue. PedsQL-F is considered to have good reliability and validity in children and young adults[178, 179].

Pain catastrophizing

In Studies III and IV, pain catastrophizing was measured using the Pain Catastrophizing Scale — Child version (PCS-C)[180]. The PCS-C is a self-assessment form, in which the children fill out the questionnaire, consisting of 13 statements that are graded on a five-point scale, from 0 = "not at all" to 4 = "very much." The maximum total score is 52 points; higher scores indicate a higher level of catastrophizing thoughts. In line with a previous study using the PCS-C to investigate pain catastrophizing in children and their parents, PCS-C scores are typically categorized into "low" (0–14 points), "medium" (15–25 points), and "high" (26–52 points) levels of estimated catastrophizing[180, 181]. To compare differences between groups regarding hypermobility measures, questionnaire scores, and physical activity, we used total scores and did not use any cutoffs.

Anxiety and depression

In Study III, anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS)[182]. The HADS is a self-assessment form developed to measure anxiety and depression in patients in somatic care. It consists of 14 statements, rated on a four-point scale from 0 to 3 points, with seven statements for each of two subscales: HADS Anxiety and HADS Depression. Participants are asked, with reference to the past week, for example, how often they felt "as if something awful was about to happen" and whether they "still enjoy the things they used to enjoy." The scores for the seven different statements on each subscale are combined, meaning that the maximum score on a subscale is 21 points. Subscale scores are interpreted as follows: 0–7 points: does not indicate anxiety or depression; 8–10 points: might suggest the presence of anxiety or depression; 11 points or more: probable depression or anxiety of clinical significance. To compare differences between groups with regard to hypermobility measures and questionnaire scores, we used total scores and did not use any cutoffs.

Statistical methods

Statistical methods

Statistical analyses were performed with IBM SPSS Statistics 18 in Study I, with IBM SPSS Statistics 25 in Study II, and with IBM SPSS Statistics 28 in Studies III and IV. An overview of the statistical methods used in this thesis is presented in Table 9.

Table 9. Statistical methods used in this thesis — an overview

Statistical method	Study I	Study II	Study III	Study IV
Descriptive statistics				
Mean and standard deviation	x			
Median and interquartile range		x	x	x
Numbers and percentages	x	x	x	x
Control for normal distribution				
Shapiro–Wilk test			x	x
Probability–Probability plot			x	x
Non-parametric tests				
Mann–Whitney U test	x		x	x
Wilcoxon Signed-Rank Test			x	
Regression analysis				
ANCOVA	x			
General linear models			x	x
Correction for multiple testing				
Bonferroni test			x	

Abbreviation: ANCOVA = analysis of covariance.

Descriptive statistics

The characteristics of the participants are presented using means and standard deviations (SD) for normally distributed data; medians and interquartile ranges (IQR) for non-normally distributed data; and frequencies/numbers and percentages where appropriate. The distribution of the data was tested in Studies III and IV by evaluating the null hypothesis of normal distribution with the Shapiro–Wilk test and using Probability–Probability plots (P–P plots).

Non-parametric tests

The Mann–Whitney U test was used to analyze statistically significant differences between groups for ordinal data. This test is a non-parametric test that compares differences between two independent groups when the dependent variable is either ordinal or continuous, but not normally distributed. The Wilcoxon Signed-Rank Test was performed to analyze differences in PPTs before and after exercise within the same group. This test is a non-parametric test that compares two related samples, matched samples, or repeated measurements on a single sample to assess whether their population mean ranks differ.

Regression analysis

An analysis of covariance (ANCOVA) was used in Study I with group affiliation as the dependent variable and balance, pain, and activity as covariates. ANCOVA is used to compare one or more mean differences while controlling for the variance associated with one or more covariates that might affect the dependent variable.

In Studies III–IV, general linear models were used for the different research questions (Table 10). The general linear model is a flexible statistical model that can model various types of relationships between a dependent variable and one or more independent variables. To control for normal distribution, the standardized residuals were presented in a P–P plot. For residuals that were found to have a skewed distribution, a log-transformation was applied to the dependent variable before it was entered into the model. This step was intended to make the residuals more normally distributed, which is important for the accuracy of the model (Figure 8A, 8B). However, log-transformation could not be used for zero or negative values, as this would have required adjustments that might have impacted the dataset. For this reason, log-transformation was not used for the effect of EIH.

Table 10. General linear models used in Studies III–IV

Model	Dependent variable	Independent variables
Study III	Each PPT and EIH measurement point separately	Age, sex, Body Mass Index, group affiliation
Study IV Model 1	Each category of physical-activity intensity separately Day and nighttime activity separately	Age, sex, group affiliation
Study IV Model 2	Physical activity	Age, sex, PCS-C, fatigue, group affiliation
Study IV Model 3	Fatigue	Age, sex, PCS-C, nighttime activity, group affiliation

Abbreviations: EIH = exercise-induced hypoalgesia; PCS-C = Pain Catastrophizing Scale — Child version; PPT = pain-pressure threshold.

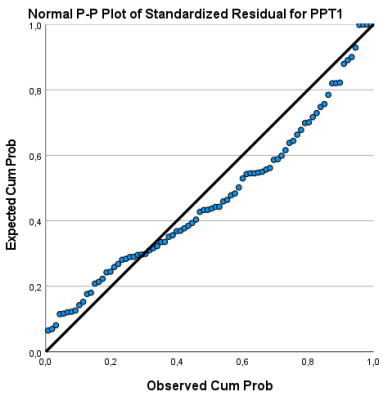


Figure 8A. Example of a Probability–Probability plot with skewed residuals where the dependent variable would be log-transformed before recalculation.

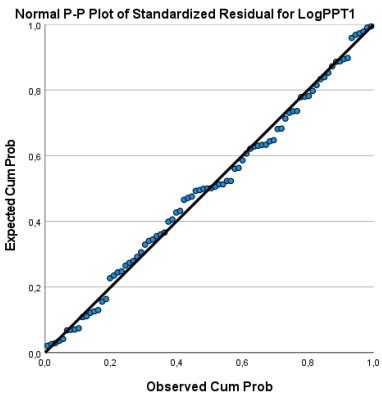


Figure 8B. Example of a Probability–Probability plot showing normally distributed residuals. Same data as in Figure 8A, after log-transformation.

Model in Study III: A general linear model, with each PPT and EIH variable as the dependent variable and age, sex, Body Mass Index (BMI), and group affiliation as independent variables, was used to test differences between groups for each PPT and EIH measurement point separately.

Model 1, Study IV: A general linear model, with physical activity as the dependent variable and age, sex, and group affiliation as independent variables, was used to test differences between groups for each category of physical-activity intensity separately. Day and nighttime activity were analyzed separately in the same model.

Model 2, Study IV: A general linear model, with physical activity as the dependent variable and age, sex, PCS-C, fatigue, and group affiliation as independent variables, was used to test for an association between fatigue and each category of physical-activity intensity.

Model 3, Study IV: A general linear model, with fatigue as the dependent variable and age, sex, PCS-C, nighttime activity, and group affiliation as independent variables, was used to test for an association between sleep movements and fatigue.

For Models 2 and 3 in Study IV, the results are presented with *p* values calculated using robust standard errors to adjust for heteroskedasticity.

Estimates of effect size are provided by Cohen's *d* for the Mann–Whitney U test and the Wilcoxon Signed-Rank Test, and in part by η^2 and R^2 for the different general linear models. For the magnitude of effect sizes, the following thresholds for Cohen's *d* were applied: 0.2 = small effect, 0.5 = medium effect, and 0.8 = large effect. For η^2, the following thresholds were used: 0.01 = small effect, 0.06 = medium effect, and 0.14 = large effect[183].

In study III the Bonferroni test was used for correction of multiple testing for cognitive and emotional factors.

Ethical considerations

Ethical considerations

The studies included in this thesis were conducted in accordance with the Helsinki Declaration and approved by the Swedish Ethical Review Authority prior to commencement (Registry numbers 393-09 and 2019-03446). Following the feasibility study (Study II), an amendment application was submitted to the Swedish Ethical Review Authority regarding adjustments in the recruitment process and minor changes in the background questions, the need for which had become apparent during the study (Registry number 2022-03780-02).

"Good research practice" refers broadly to the collective ethical standards that researchers must follow in their professional role[184, 185]. Upholding good research practice involves a responsibility to comply with ethical frameworks, including adherence to laws and established norms in research[184, 185]. In line with this, the study protocol for Study II was registered with Researchweb.org (project number 270501), and the joint study protocol for Studies II–IV was registered with ClinicalTrials.gov (NCT05633225). Such registration increases transparency and ensures that a study will not be surreptitiously altered during its course, which enhances the accuracy of the results. When changes to one study protocol were necessary, an amendment was submitted for ethical review prior to data collection.

To prevent measurement bias, the investigators who assessed the participants were blinded to group affiliation. Additionally, data entry was conducted by two individuals to minimize the risk of errors during data transfer. Participants in the control group were partially recruited through family, friends, and colleagues of the research team. This introduces a risk that the group may not be fully representative. However, given the difficulties encountered in recruitment, this was a feasible solution, and it was also openly reported when the results were published. Without this approach, it would not have been possible to recruit a control group, which would have made comparisons impossible. Acknowledging such difficulties makes it more likely that the research team will be able to maintain a professional and ethical approach toward data collection and the handling of the material.

All participants were thoroughly informed about the purpose of the study, including the assessments, examinations, and questionnaires. They were given the opportunity to ask questions and provided with contact details for the researchers responsible. To ensure comprehension regardless of age, the information was tailored to four different age groups: 8–10, 11–12, 13–14, and 15–17 years. All participants gave their assent/consent to participate.

One ethical concern relates to waste of time. Although the risk of this in our studies was low, our research did require the participants and their guardians to devote time and resources to it. Participants initially were not going to receive any compensation for their participation, because we deemed it important for the adolescents to participate voluntarily and not be influenced by financial incentives. Some potential participants who chose not to participate stated that the absence of compensation was unreasonable given the time investment required. For this reason, we sought approval to include a cinema ticket as a token of appreciation in the amendment application, so that the adolescents could be informed of this when deciding whether to participate.

Participation in research can increase people's awareness of their own situation. When necessary, healthcare professionals were available to address follow-up questions and discuss any thoughts that came up. Where applicable, participants were referred to appropriate healthcare services.

Another ethical concern was that some of the instruments and measurements used in the studies — although they had been chosen based on current research to answer the research questions — may cause minor discomfort or lead to a feeling of failure. For example, balance testing could remind the adolescents of their difficulties. However, we made sure that the participants felt successful regardless of test outcome. Further, wearing a visible activity monitor can be embarrassing and disruptive in daily life. We tried to make wearing the monitor as easy as possible by attaching it to the leg, so that participants would not have to think about it too often.

Medical treatment of children with chronic pain has proven to be a very challenging task. The pain medications available on the market have only

limited efficacy for these patients, which might be due to central sensitization affecting pain interpretation. This thesis aims for an enhanced understanding of the patient's situation and possible underlying causes that may hinder successful treatment. Against this background, we conclude that the project involves only a low risk of discomfort to individual participants, and that the societal benefits of the knowledge potentially gained outweigh the minimal risk to the individuals involved in our studies.

Experimental pain measurements in a patient group with chronic pain can increase the risk of altered pain perception. To minimize negative experiences, we provided a thorough explanation of each task to ensure that all adolescents understood them. The participants were in control of the pressure used during pain tests, meaning that they could stop if they felt uncomfortable. Cycling on an ergometer could be associated with discomfort, and for this reason participants were allowed to stop if they experienced muscle strain or shortness of breath.

It is important that any research conducted should have significant potential benefits — in our case, for the patient group concerned. The main benefit of participating in this study for individual participants is the opportunity to influence future healthcare by increasing knowledge about adolescents with HSD/hEDS. Additionally, participants had an opportunity to share their experiences with each other, which is often perceived as meaningful. Another benefit is the possibility that the results may help individuals in this patient group to better understand their chronic pain in the long term.

Understanding and treating pain in adolescents is crucial, since they run an increased risk of chronic pain in adulthood[117]. Using experimental methods to study early pain experiences and identify biopsychosocial risk factors in adolescence will enhance our understanding of how and why chronic pain develops later in life[186]. Experimental pain research has already significantly contributed to our ability to understand and treat pain in adults. Denying adolescents the opportunity to participate in such research would prevent those benefits from materializing. If we do not understand the underlying factors causing pain in adolescents with hypermobility, they risk being mistreated for their type of pain, which will — unnecessarily — increase their suffering.

Results

Results

Study I

The study aimed to assess and compare hypermobility, balance, pain, activity, and participation between a group of adolescents with HSD/hEDS and a healthy control group.

Participant demographics: Twenty adolescents with HSD/hEDS aged 8–15 years (mean age 11.2 years, SD 1.9), including 8 girls and 12 boys, were compared with a healthy control group of 24 children aged 8–15 years (mean age 11.4 years, SD 2.0), consisting of 11 girls and 13 boys.

Hypermobility: The Del Mar Scale showed a significant difference in hypermobility scores ($p < 0.001$), with the HSD/hEDS group having a mean score of 6.7 (SD 1.9) and the control group a mean score of 3.8 (SD 1.6). Information about the joints evaluated and the number of adolescents who were hypermobile in each joint in the two groups is presented in Table 11.

Table 11. Evaluations of hypermobility using the Del Mar Scale

Joint	HSD/hEDS group (n = 20) Number (%)		Control group (n = 24) Number (%)	
Hyperflexion thumb	**13**	(65)	**3**	(13)
Hyperextension fifth finger	**9**	(45)	**2**	(8)
Hyperextension elbow	**14**	(70)	**5**	(21)
Outward rotation shoulder	**20**	(100)	**18**	(75)
Trunk flexion	**0**	(0)	**2**	(8)
Hip abduction	**13**	(65)	**11**	(46)
Patella movement	**17**	(85)	**13**	(54)
Hyperextension knee	**18**	(90)	**8**	(33)
Hyperflexion knee	**20**	(100)	**24**	(100)
Dorsal extension feet	**1**	(5)	**0**	(0)
Hyperextension big toe	**8**	(40)	**5**	(21)

Balance: The BOT-2 assessment showed a significant difference in balance, with the HSD/hEDS group scoring a mean of 14.7 (SD 4.0), as against 20 (SD 3.3) in the control group ($p < 0.001$).

Participation: The Frequency of Participation Questionnaire (FPQ) indicated that the HSD/hEDS group participated less often than the control group in activities such as housework ($p = 0.004$), cycling ($p = 0.001$), and sports and outdoor games ($p = 0.05$). Ten children in the HSD/hEDS group required daily rest, as against two in the control group ($p = 0.001$). On the other hand, the HSD/hEDS group reported a higher frequency of participation in non-sport games ($p = 0.03$).

Pain characteristics: Eighteen adolescents in the HSD/hEDS group and 24 in the control group completed the pain drawing and the pain and activity diary. All but one adolescent in the HSD/hEDS group reported pain, primarily in the feet and knees, but also in the wrists and shoulders. In contrast, 11 adolescents in the control group reported pain, mostly related to muscle soreness or minor injuries. Pain intensity was significantly higher in the HSD/hEDS group ($p < 0.001$), with a mean NRS score of 3.6 (SD 1.6), as against 1.9 (SD 1.0) in the control group.

The differences between the groups in reported pain, pain intensity, limitation of participation in activity because of pain, hours of activity, and degree of activity over two weeks are presented in Table 12.

In a multiple regression analysis with group affiliation as the dependent variable, statistically significant differences were found between the HSD/hEDS group and the control group, with the HSD/hEDS group showing poorer balance, lower physical activity, and higher pain intensity (Table 13).

Table 12. Mean, SD, and range in the HSD/hEDS and control groups regarding reported pain, pain intensity, limitation of participation in activity because of pain, hours of activity, and degree of activity over two weeks

	HSD/hEDS group (n = 18) Mean (SD)	**Control group (n = 24)** Mean (SD)	***p* value**
Number of reported pain hours	133 (121)	11 (19)	**< 0.001***
Overall pain-intensity scale (score)	3.6 (1.6)	1.9 (1.0)	**< 0.001***
Number of days with limited activity participation owing to pain	7 (6)	1 (1)	**< 0.001***
Number of reported activity hours	10 (6)	18 (7)	**< 0.001***
Degree of activity	1.7 (0.7)	2.5 (0.6)	**< 0.001***

*Statistically significant at $\alpha = 0.05$.

Table 13. Analysis of differences between groups in affected balance according to the BOT-2, the degree-of-activity scale, and the pain-intensity scale

Variable	**Standard error**	**Beta**	***p* value**	**95 % confidence interval**
Balance	0.013	0.389	**0.002***	0.017–0.070
Degree of activity	0.077	0.310	**0.011***	0.049–0.359
Pain intensity	0.038	-0.305	**0.011***	(-0.176)–(-0.024)

Dependent variable: Group. *Statistically significant at $\alpha = 0.05$.

Study II

The study aimed to investigate the feasibility of a study protocol for detecting the presence of signs of central sensitization through primary and secondary hyperalgesia, endogenous pain modulation and exercise-induced hyperalgesia (EIH) in a group of adolescents with HSD/hEDS compared with a healthy control group.

Participant recruitment: Out of 136 patients identified as potential participants in the patient group, 57 met the inclusion criteria and were invited to participate. Of these, thirteen patients, aged 13–17 years, eventually agreed to participate, but three of them were later excluded (Appendix 2).

Control-group recruitment: Six schools were contacted, but this did not yield a single healthy adolescent for the control group. Nine age- and sex-matched healthy adolescents were eventually recruited through convenience sampling (Appendix 3).

Descriptive data on the study population are given in Table 14.

Table 14. Description of the study population

		HSD/hEDS group (n = 10) Median (range)	**Control group (n = 9)** Median (range)
Age (years)		15 (13–17)	15 (14–17)
Beighton score (0–9)		4 (2–8)	4 (2–9)
BMI (kg/m²)		19 (17–29)	20 (19–24)
Reported number of occasions of planned physical activity per week		0.5 (0–3)	0 (0–2)
		Number	Number
Sex	Male	4	4
	Female	6	5

Abbreviation: BMI = Body Mass Index.

Reported pain: The HSD/hEDS group reported higher median pain intensity, as rated using the NRS, over the week prior to measurement (3.5, range 0–8) than the control group (0, range 0–3). The same was evident regarding the day of assessment, with the HSD/hEDS group scoring 1.5 (range: 0–5) and the control group 0 (range: 0). Seven participants in the patient group reported that their pain was severe enough to prevent them from fully engaging in

their educational activities. As regards pain location, multiple body parts were reported, especially in the lower extremities. In contrast, the control group reported minimal pain and fewer pain locations (Table 15).

Table 15. Pain demographics

	HSD/hEDS group (n = 10)	**Control group (n = 9)**
Pain intensity (NRS)	Median (range)	Median (range)
Over the week prior to measurement	3.5 (0–8)	0 (0–3)
At the time of assessment	1.5 (0–5)	0 (0)
Pain duration	Number	Number
No pain	0	4
Less than 3 months	1	1
1.5 years	2	2
More than 5 years	7	2
Pain localization	Number	Number
Legs (unspecified)	5	0
Hips	4	0
Knees	5	3
Feet/toes	9	1
Shoulder/neck	7	1
Hands/wrists	3	1
Back/torso	3	0
Stomach	3	1

Abbreviation: NRS = Numerical Rating Scale.

Feasibility of measuring central sensitization: All assessments were well tolerated, and no adverse reactions were reported. However, in both groups there were participants who did not achieve the expected pain response in the tests of conditioned pain modulation and EIH. Only one patient discontinued cycling owing to leg fatigue.

Study III

This study aimed to explore signs of central sensitization, including EIH, and examine fatigue severity in adolescents with HSD/hEDS.

Participant recruitment and demographics: Out of 176 adolescents with HSD/hEDS and 111 healthy adolescents invited, 37 adolescents with HSD/hEDS and 47 healthy adolescents were included in the final analysis (Appendix 2 and 3). No statistically significant differences were found between the groups in sex distribution or BMI, but the adolescents with HSD/hEDS were older (p = 0.017) and had, as expected, higher Beighton scores (p < 0.001) (Table 16).

Table 16. Description of the study population in Study III

		HSD/hEDS group (n = 37) Median (IQR)	**Control group (n = 47)** Median (IQR)	**Test statistics** [a]	***p* value** [a]
Age (years)		16.4 (14.8–17.0)	15.3 (14.0–16.2)	615.5	**0.022***
Beighton score, 0–9		6 (4–7)	2 (1–4)	314	**< 0.001***
Beighton score, males		5 (2–6) $^{n = 10}$	1 (0–3) $^{n = 13}$	18.5	**0.003***
Beighton score, females		6 (4–7) $^{n = 27}$	2 (2–4) $^{n = 34}$	164.5	**< 0.001***
Height (m)		1.7 (1.6–1.7)	1.7 (1.6–1.8)	701.5	0.130
Weight (kg)		58.5 (50.8–72.9)	59 (52.1–67.5)	854	0.889
BMI (kg/m²)		21.2 (18.5–25.6)	20 (18.9–23.4)	732.5	0.217
		Number (%)	Number (%)		
Sex	Male	10 (27)	13 (28)	864	0.949
	Female	27 (73)	34 (72)		
Occasions of planned physical activity/week (Number (%))					
0		10 (27.0)	12 (25.5)		
1–2		18 (48.6)	12 (25.5)		
≥3		9 (24.3)	23 (48.9)		

Abbreviations: BMI = Body Mass Index; IQR = interquartile range.
Note: [a] Mann–Whitney U Test — group differences; *Statistically significant at α = 0.05.

Pain characteristics: The adolescents with HSD/hEDS reported significantly higher pain intensity both over the week prior to measurement ($p < 0.001$) and at the time of assessment ($p < 0.001$) than the control group. Most adolescents in the control group reported no pain (75%) or only local pain (25%), while those with HSD/hEDS commonly reported widespread pain (60%) (Table 17).

Table 17. Pain characteristics of the study population in Study III

	HSD/hEDS group (n = 37) Median (IQR)	**Control group (n = 47)** Median (IQR)	**Test statistics** [a]	**Estimate of effect size** [b]	***p* value** [a]
Pain intensity (NRS)					
Over the past week	5 (3–6)	0 (0–2)	114.5	2.215	**< 0.001***
At the assessment	3 (2–5)	0 (0–0)	132.5	2.102	**< 0.001***

	HSD/hEDS group (n = 37) Number (%)	**Control group (n = 47)** Number (%)
Pain duration		
No pain	0	33 (70)
Less than 3 months	0	3 (6)
3–6 months	1 (3)	3 (6)
More than 6 months	36 (97)	8 (17)
Pain frequency		
No pain	1 (3)	26 (55)
Once or twice each month	5 (14)	9 (19)
Several times each month	0	12 (26)
Several times each week	6 (16)	0
Several times each day, persistent	25 (68)	0
Pain localization [c]		
No pain	1 (3)	35 (75)
Local pain [d]	6 (16)	12 (25)
1–2 body quadrants [e] and/or axial regions [f] (at least 5 locations)	8 (22)	0
Widespread pain = pain in 3 or more body quadrants and/or axial regions (at least 5 locations)	22 (60)	0

Abbreviations: NRS = Numerical Rating Scale; IQR = interquartile range.
Notes: [a] Mann–Whitney U Test — group differences; [b] Cohen's *d*. [c] Pain drawing, localization of pain in the past 3 months. [d] Local pain = pain in a maximum of 2 joint pairs, 1 joint pair and 1 axial region, or a maximum of 3 axial regions. [e] Body quadrants = upper–lower/left–right side of the body. [f] Axial regions = cervical spine, chest, thoracic spine, lower back, and stomach. *Statistically significant at $\alpha = 0.05$.

Pain measurements: The adolescents with HSD/hEDS demonstrated generalized hyperalgesia, with significantly lower pressure-pain thresholds (PPTs) across all examined muscle groups than the control group (trapezius: $p < 0.001$; deltoideus: $p = 0.015$; tibialis anterior: $p = 0.045$; and paraspinal muscles of the lower back: $p = 0.021$). Further, significant differences were also observed between groups in PPTs after exercise for two muscle groups: trapezius: $p = 0.001$; and tibialis anterior: $p < 0.008$. PPTs were again lower in the HSD/hEDS group (Table 18, Figure 9).

Table 18. Signs of generalized hyperalgesia and exercise-induced hypoalgesia

	HSD/hEDS group (n = 37) Median (IQR)	**Control group (n = 47)** Median (IQR)	**Partial η^2**	***R*²**	***p* value**
Pressure-pain threshold (kg/cm²), primary and secondary hyperalgesia					
Trapezius muscle	2.06 (1.57–3.07)	3.68 (2.33–4.54)	0.156	0.165	**< 0.001***
Tibialis anterior	3.82 (2.59–6.1)	5.31 (3.64–7.97)	0.050	0.058	**0.045***
Deltoideus muscle	1.77 (1.07–2.52)	2.31 (1.42–3.91)	0.072	0.096	**0.015***
Lower back, L3	2.66 (1.73–5.78)	4.27 (2.56–5.95)	0.065	0.078	**0.021***
Pressure-pain threshold (kg/cm²) after exercise					
Trapezius muscle	2.26 (1.61–3.13)	3.73 (2.14–5.37)	0.154	0.164	**< 0.001***
Tibialis anterior	4.85 (3.26–7.60)	6.47 (4.70–9.65)	0.087	0.092	**0.008***

Abbreviations: IQR = interquartile range; L3 = Lumbar vertebra No. 3.
Note: Between-group statistics: [a] Based on log data, adjusted for age, sex, Body Mass Index, and group affiliation. *Statistically significant at $\alpha = 0.05$.

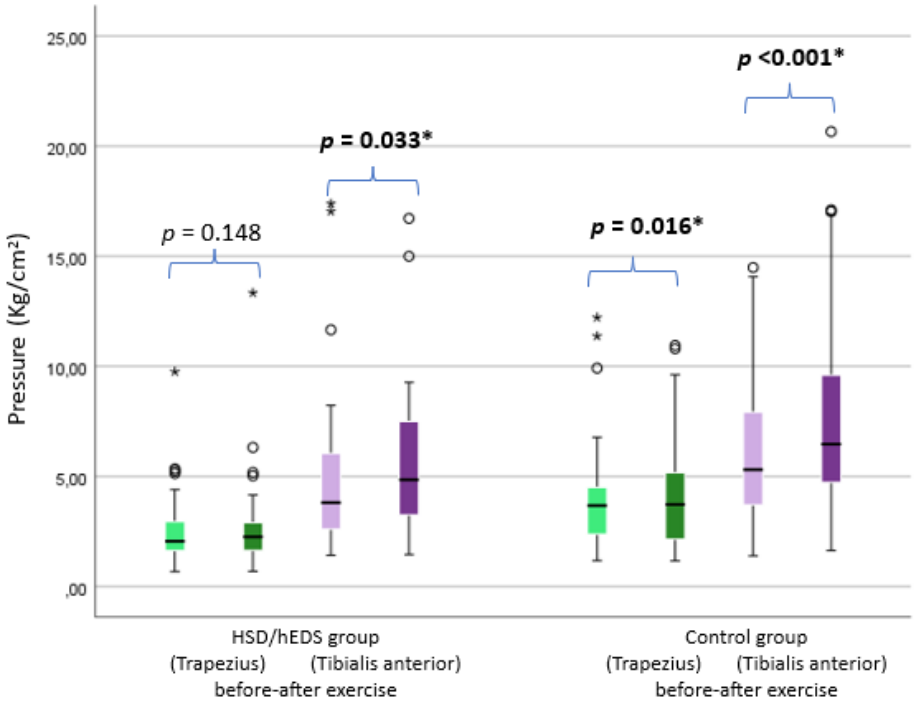


Figure 9. Pressure-pain thresholds (PPT) before and after exercise per muscle group and group affiliation.

o = outliers, ★ = extreme outliers; Mann–Whitney U test — within-group statistics; *Statistically significant at α = 0.05.

In both groups, post-exercise increases in PPTs were observed. In the HSD/hEDS group, no statistically significant difference was found for the trapezius muscle between pre-exercise and post-exercise PPT measurements (p = 0.148), but a significant increase in PPT was found for the tibialis-anterior muscle (p = 0.033). In the control group, PPTs increased significantly both at the trapezius muscle (p = 0.016) and at the tibialis-anterior muscle (p < 0.001) (Table 19).

Table 19. Pressure-pain thresholds (PPT) before and after exercise — differences within groups

	PPT before exercise Median (IQR)	**PPT after exercise** Median (IQR)	**Z value** [a]	**Estimate of effect size** [b]	***p* value** [a]
Trapezius muscle					
HSD/hEDS group (n = 37)	2.06 (1.57–3.07)	2.26 (1.61–3.13)	-1.448	0.490	0.148
Control group (n = 47)	3.68 (2.33–4.54)	3.73 (2.14–5.37)	- 2.398	0.747	**0.016***
Tibialis-anterior muscle					
HSD/hEDS group (n = 37)	3.82 (2.59–6.10)	4.85 (3.26–7.60)	-2.127	0.746	**0.033***
Control group (n = 47)	5.31 (3.64–7.97)	6.47 (4.70–9.65)	-4.507	1.745	**< 0.001***

Abbreviation: IQR = interquartile range.
Note: [a] Wilcoxon Signed-Rank Test — within-group differences; [b] Cohen's *d;* *Statistically significant at α = 0.05.

As regards the difference between the pre-exercise and post-exercise PPT measurements, which is deemed to reflect the effect of EIH, the HSD/hEDS group exhibited a less pronounced increase in PPTs than the control group. This suggests a reduced effect of EIH in the tibialis-anterior muscle (p = 0.019) However, there were no statistically significant differences between the groups in the trapezius muscle (p = 0.636) (Table 20, Figure 10).

Table 20. Signs of generalized hyperalgesia and exercise-induced hypoalgesia

	HSD/hEDS group (n = 37) Median (IQR)	Control group (n = 47) Median (IQR)	Test statistic [a]	Estimate of effect size [b]	*p* value [a]
Exercise-induced hypoalgesia effect (kg/cm²)					
Trapezius muscle	0.10 ([-0.24]– 0.58)	0.25 ([-0.12]–0.57)	817	0.103	0.636
Tibialis anterior	0.33 ([-0.31]–1.22)	1.30 (0.08–2.38)	610	0.528	**0.019***

Abbreviations: IQR = interquartile range.
Note: Between-group statistics: [a] Mann–Whitney U Test — group differences. [b] Cohen's *d*; *Statistically significant at α = 0.05.

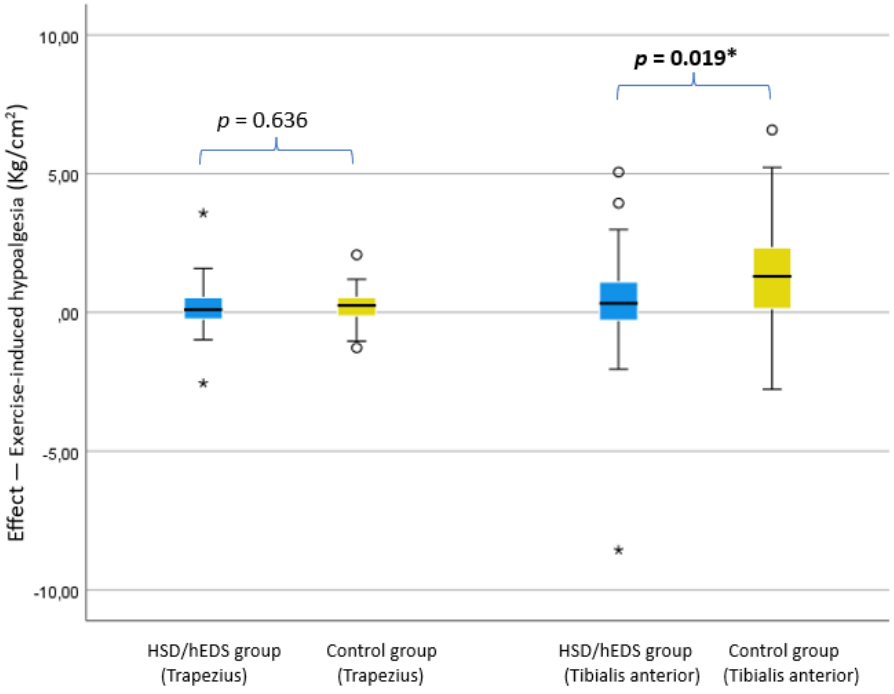


Figure 10. Effect of exercise-induced hypoalgesia — differences between groups.
o = outliers, ★ = extreme outliers; Mann–Whitney U test — group differences; *Statistically significant at α = 0.05.

Cognitive and emotional factors: Adolescents with HSD/hEDS had significantly higher levels of fatigue (PedsQL-F — general fatigue: $p < 0.001$; PedsQL-F — sleep/rest fatigue: $p = 0.007$; PedsQL-F — cognitive fatigue: $p < 0.001$), significantly higher scores for pain catastrophizing (PCS-C: $p < 0.001$), and significantly higher HADS depression scores ($p < 0.010$) and HADS anxiety scores ($p = 0.007$) than the control group (Table 21).

Table 21. Results for cognitive and emotional factors, by group

	HSD/hEDS group (n = 37) Median (IQR)	**Control group (n = 47)** Median (IQR)	**Test statistic** [a]	**Estimate of effect size** [b]	***p* value** [a]
PedsQL MFS general fatigue, 0–100	33 (21–46)	75 (58–92)	141.5	2.05	**< 0.001***
PedsQL MFS sleep/rest fatigue, 0–100	46 (31–56)	63 (46–75)	475.0	0.84	**0.007***
PedsQL MFS cognitive fatigue, 0–100	46 (33–58)	75 (58–88)	375.0	1.11	**< 0.001***
PCS-C, 0–52	17 (12–28.5)	4 (1–10)	234.0	1.60	**< 0.001***
HADS depression, 0–21	11 (7.5–15)	6 (2–10)	392.0	1.063	**< 0.001***
HADS anxiety, 0–21	5 (4–8.5)	2 (1–5)	396.5	1.05	**0.007***

Abbreviations: IQR = interquartile range; PedsQL-MFS = Pediatric Quality of Life Multidimensional Fatigue Scale; PCS-C= Pain Catastrophizing Scale — Child version; HADS = Hospital Anxiety and Depression Scale.
Notes: [a] Mann–Whitney U — group differences; [b] Cohen's *d*; *Statistically significant at α = 0.05; Bonferroni significant at $a = 0.008$.

Study IV

This study primarily aimed to explore, using accelerometers, daytime and nighttime movement behavior in adolescents with HSD/hEDS as compared with a healthy control group. A secondary focus was to examine the

relationship between fatigue and movement behavior, considering pain catastrophizing as a potentially confounding factor.

Participant recruitment and demographics: The same cohort as in Study III was used. Of the 49 adolescents with HSD/hEDS and 51 healthy adolescents invited, 37 adolescents with HSD/hEDS (Appendix 2) and 45 healthy adolescents participated (Appendix 3). This yielded 323 recorded 24-hour periods for the HSD/hEDS group and 402 for the control group. There were no significant differences between the groups in terms of sex distribution or BMI, although the HSD/hEDS group was slightly older ($p = 0.028$) and had higher Beighton scores ($p < 0.001$) (Table 22).

Table 22. Description of the study population in Study IV

		HSD/HEDS group (n = 37)	Control group (n = 45)	Test statistic [a]	*p* value [a]
		Number (%)	Number (%)		
Sex	Male	10 (27)	11 (24)	811.0	0.80
	Female	27 (73)	34 (76)		
		Median (IQR)	Median (IQR)		
Age (years)		16.4 (14.8–17.1)	15.4 (14.1–16.3)	597.0	**0.03***
Beighton score (0–9)		6 (4–6)	2 (1–4)	314.0	**< 0.001***
Beighton score males		5 (2–6) [n = 10]	1 (0–3) [n = 11]	18.5	**0.01***
Beighton score females		6 (4–7) [n = 27]	2 (2–4) [n = 34]	164.5	**< 0.001***
Height (cm)		167.0 (160.8–172.5)	169.0 (164.0–174.4)	694.5	0.20
Weight (kg)		58.5 (50.8–72.9)	57.8 (51.9–68.2)	807.0	0.81
BMI (kg/m²)		21.2 (18.5–25.6)	20.1 (18.9–23.4)	707.5	0.24

Abbreviations: BMI = Body Mass Index; IQR = interquartile range.
Notes: [a] Mann–Whitney U test statistic for group differences; *Statistically significant at $\alpha = 0.05$.

Pain characteristics: Pain was statistically significantly more prevalent in the HSD/hEDS group over the week prior to measurement ($p < 0.001$). While most adolescents in the control group reported either no pain (78%) or localized pain (22%), most adolescents in the HSD/hEDS group experienced pain in

multiple body quadrants (22%) or widespread pain (57%). All HSD/hEDS participants reported chronic pain lasting more than three months (100%), whereas the control participants mostly reported no pain duration (71%) or shorter-duration pain (11%).

Movement behavior: During the day, the HSD/hEDS group spent statistically significantly more time in sedentary behavior (p = 0.010) and less time in moderate-to-vigorous physical activity ($p < 0.001$) compared with the control group. The median daily time spent in moderate-to-vigorous physical activity was 20 minutes for the HSD/hEDS group, as against 32 minutes for the control group. At night, the HSD/hEDS group had statistically significantly more sleep movements than the control group (p = 0.034) (Table 23, Figure 11a, 11b)

Table 23. Time spent at different levels of activity intensity

Category	HSD/hEDS group (n = 37) Median (IQR)	Control group (n = 45) Median (IQR)	Partial η^2	R^2	*p* value
Sleep (minutes/day)	914.5 (854.5–957.0)	916,7 (896.7–969.4)	0.081	0.15	**0.01***
Sedentary behavior (minutes/day)	457.9 (457.9–502.2)	414.0 (382.6–452.7)	0.146	0.15	**< 0 001***
Light-intensity physical activity (minutes/day)	55.1 (39.6–70.9)	65.5 (49.0–72.5)	0.007	0.15	0.46
Moderate-to-vigorous physical activity (minutes/day)	19.7 (19.7–26.0)	31.9 (24.2–44.3)	0.179	0.30	**< 0.001***
Sleep movement (percent of nighttime)	3.4 (2.8–4.9)	3.0 (2.2–3.7)	0.056 ♦	0.13 ♦	**0.03*♦**

Abbreviation: IQR = interquartile range.

Note: General linear model statistics; *Statistically significant at α = 0.05, data adjusted for age and sex; ♦ based on log-data.

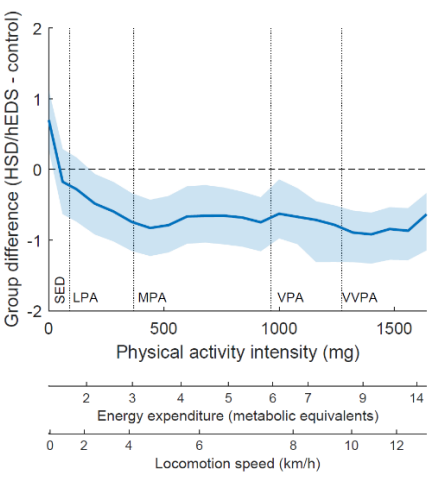


Figure 11a. Daytime physical-activity pattern.

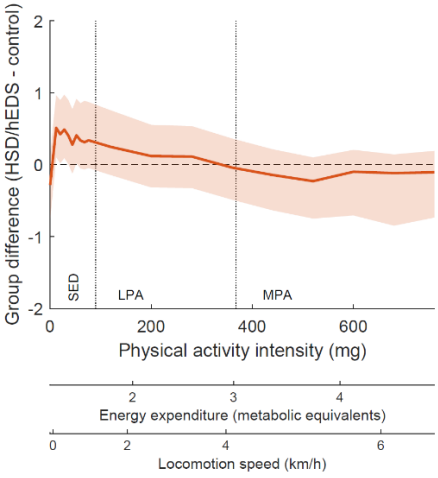


Figure 11b. Nighttime physical-activity pattern.

Abbreviations: mg = milligravity; SED = sedentary behavior, LPA = light physical activity, MPA = moderate physical activity, VPA = vigorous physical activity, VVPA = very vigorous physical activity.

Notes: Figure 1a and 1b shows disparity in activity levels as broken down into daytime and nighttime. While positive values on the y-axis represent higher activity levels in the patient group, negative values reflect higher activity levels in the control group. The solid blue and orange lines represent the median differences between the two groups, and the light blue and light orange areas indicate the confidence intervals (95%). All values are expressed in terms of standard deviations.

Fatigue and pain catastrophizing: The adolescents with HSD/hEDS perceived more fatigue (had a lower PedsQL-F score; $p < 0.001$) and more pain catastrophizing (had a higher PCS-C score; $p < 0.001$) than the control group (Table 24). While there was no statistically significant association between fatigue and daily sedentary behavior, moderate-to-vigorous physical activity, or sleep movements, there was a significant association between fatigue and pain catastrophizing, with higher scores for pain catastrophizing linked to greater perceived fatigue ($p < 0.001$; $\beta = -2.720$).

Table 24. Descriptive data for the questionnaire investigating fatigue and catastrophizing

	Patient group (n = 37) Median (IQR)	**Control group (n = 45)** Median (IQR)	**Test statistic** [a]	**Estimate of effect size** [b]	***p* value** [a]
PedsQL-F total score	125 (90–161)	217 (167–240)	216.0	1.64	**< 0.001***
PedsQL-F general fatigue	33 (21–46)	75 (63–92)	130.5	2.09	**< 0.001***
PedsQL-F sleep/rest fatigue	46 (31–56)	63 (44–75)	448.0	0.86	**< 0.001***
PedsQL-F cognitive fatigue	46 (33–58)	75 (58–88)	350.0	1.14	**< 0.001***
PCS-C total score	17 (12–29)	4 (0.5–10)	205.0	1.69	**< 0.001***
PCS-C rumination	7 (4–11)	2 (0–5)	294.0	1.33	**< 0.001***
PCS-C magnification	3 (1–5)	0 (0–2)	388.0	1.03	**< 0.001***
PCS-C helplessness	8 (5–11)	1 (0–3)	177.0	1.83	**< 0.001***

Abbreviations: IQR = interquartile range; PedsQL-F = Pediatric Quality of Life Inventory — Multidimensional Fatigue Scale, child version; PCS-C = Pain Catastrophizing Scale — Child version.

Notes: [a] Mann–Whitney U test statistic for group differences. [b] Cohen's *d* for effect size; *Statistically significant at $\alpha = 0.05$.

Discussion

Discussion

The overall aim of this thesis was to better understand pain and its impact on the ability to function in adolescents with HSD/hEDS. The findings highlight that adolescents with HSD/hEDS are significantly affected in their daily lives, particularly regarding pain, reduced physical activity, and limited participation. Additionally, the findings also suggest a potential link between HSD/hEDS and central sensitization. Finally, our results show that the adolescents with HSD/hEDS moved more during sleep than the adolescents of the control group.

I have organized the discussion of the findings from the overall project in terms of the impact of pain, the impact of fatigue, and the impact on physical activity in adolescents with HSD/hEDS, with a view to synthesizing those findings in order to consider clinical implications and ultimately recommend treatment approaches related to these issues.

The impact of pain

The findings of this thesis confirm the complexity of pain. Adolescents with HSD/hEDS showed significantly higher pain intensity than a control group. Moreover, pain appeared to interfere more with their daily activities, including their participation in education, which highlights the chronic and disruptive nature of pain in this population. These results are consistent with previous research, which emphasizes the pervasive and intrusive nature of pain in adolescents with HSD/hEDS, as noted by both Pacey et al.[109] and Scheper et al.[54], who found that pain significantly affects quality of life and daily functioning in children and adolescents with HSD/hEDS.

Additionally, the results of our work showed variability in pain localization among adolescents with HSD/hEDS. In Study I, adolescents with HSD/hEDS predominantly experienced pain in the lower extremities. In Study III, by contrast, such adolescents frequently reported pain in multiple body regions. In addition to the fact that the groups and individuals participating in these studies are not the same, this difference may also partly be due to the fact that we collected data in different ways: one group provided responses over

a 14-day period, while the other recalled their experiences from the past three months. Additionally, the participants in Study I were younger, which makes it possible to speculate that pain may not yet have generalized in them to the same extent as in the slightly older group in Study III. Even so, the results for the adolescents with HSD/hEDS in Study III clearly contrast with those for the respective control group, where pain was less frequent and, if present, more localized. These findings from Study III align with results from other studies that indicate an increased prevalence of chronic, generalized pain in adolescents with HSD/hEDS[54]. Generalized pain is one of several indications that the pain system is impacted, and it might be a sign of central sensitization[81].

One of the aims of this thesis was to explore and understand the impact of central sensitization as a possible pathophysiological mechanism of pain in adolescents with HSD/hEDS. As explained in the methodology section, signs of central sensitization could be explored in several ways. In Study III, we found generalized pressure hyperalgesia in the HSD/hEDS group as compared with the control group, supporting the hypothesis that adolescents with HSD/hEDS have an upregulated pain system. This finding aligns with previous studies, such as those by Rombaut et al.[81] and Scheper et al.[82], which identified reduced pressure-pain thresholds (PPTs) in both adolescents and adults with HSD/hEDS.

Signs of central sensitization were further explored using exercise-induced hypoalgesia (EIH). Our findings regarding EIH indicate that the adolescents with HSD/hEDS did not exhibit the hypoalgesia response following exercise typically seen in healthy individuals. Unlike the control group, where exercise increased pain thresholds (meaning that more pressure was needed to produce a painful sensation) in both exercised and non-exercised muscle groups, the participants with HSD/hEDS did not show a hypoalgesic response in the non-exercised muscles. However, we could not demonstrate a statistically significant difference between the groups in the effect of EIH (calculated as the difference between the PPT value before exercise and the PPT value after exercise) in the remote muscle. This might be because the intervention was not strong enough to cause measurable changes or because external factors, such as variation in the pain experienced, influenced the

results. In fact, only 60 percent of the adolescents in the HSD/hEDS group manifested widespread pain, which may have been a contributing factor in that we could not demonstrate a statistically significant difference between the groups in the effect of EIH in the remote muscle. Even so, this decreased hypoalgesia response at the exercising muscle could be related to impaired descending pain modulation, which could be a part of central sensitization[103]. This impairment might hinder the commonly pain-relieving response to exercise in individuals with HSD/hEDS. De Wandele et al.[187] further supports this observation by showing a lower pain-inhibiting effect in the exercising limb of an HSD/hEDS group as compared with a control group.

Psychological factors have been shown to contribute to increased pain sensitivity and to a reduced EIH response in both pain-free adults and adults with chronic pain[102, 188]. In Studies III and IV, cognitive-emotional factors such as increased anxiety, depression, and pain catastrophizing could be seen in adolescents with HSD/hEDS. Furthermore, adolescents with HSD/hEDS seem more susceptible to anxiety and depression-related conditions, as noted in studies by Eccles et al.[24] and Bulbena et al.[189]. The interaction between these psychological factors and central sensitization could further complicate the pain experience in this group, suggesting that it may be beneficial to take a holistic approach to pain management, addressing both physical and psychosocial aspects[190].

As regards clinical practice, the findings of this thesis suggest that clinicians should be aware of the potential for altered pain responses in individuals with HSD/hEDS, particularly in relation to physical activity. Increased sensitivity to pressure and reduced pain inhibition after exercise may indicate changes in central pain mechanisms, such as central sensitization, that extend beyond the muscles and joints. Recognizing the role of these central pain mechanisms is crucial for developing effective treatment plans that address both the physical and psychological aspects of pain in adolescents with HSD/hEDS. Additionally, exploring the role of central sensitization in the management of HSD/hEDS could lead to more effective interventions, including early therapeutic strategies and lifestyle modifications aimed at mitigating the impact of chronic pain in adolescents with HSD/hEDS.

The impact of fatigue

The findings from Studies III and IV reveal that adolescents with HSD/hEDS experience significantly higher levels of fatigue across all examined domains — general fatigue, sleep/rest fatigue, and cognitive fatigue — than the control group. This finding aligns with previous research, which consistently indicates a higher prevalence of fatigue in adolescents with chronic pain and heritable connective-tissue disorders, particularly HSD/hEDS[120]. Unlike the association between HSD/hEDS and increased fatigue reported by Sommer et al.[120], our study could not determine whether fatigue is a result of pain or whether it has an independent, separate cause. This is thus an issue that requires further investigation.

In this thesis, no significant association was found between perceived fatigue and daytime movement behaviors, such as sedentary behavior and moderate-to-vigorous physical activity. However, it was found that adolescents with HSD/hEDS scored statistically significantly higher than the control group not only on measures of fatigue but also on measures of pain catastrophizing. The observed correlation between fatigue and pain catastrophizing suggests that concern about pain experiences may contribute to the perceived fatigue in adolescents with HSD/hEDS. Pain and fatigue have both been shown to be barriers to exercise in adults with HSD/hEDS[113]. If this finding is applicable to adolescents with HSD/hEDS, we might speculate that addressing and treating pain catastrophizing could increase physical-activity levels. Also, the findings of this thesis generally underscore the importance of incorporating psychological strategies into physiotherapy interventions to ensure that adolescents with HSD/hEDS will assume more control and responsibility in their healthcare experiences, including in terms of exercise participation. This issue needs to be investigated further to identify effective methods and approaches.

Furthermore, no statistically significant association was found between sleep movement and perceived fatigue. Previous research has shown that lower sleep efficiency in adolescents with chronic pain predicts greater activity limitations, and that poor sleep is associated with the development of chronic pain, further complicating pain treatment[191, 192]. Sleep disorders, which we have not controlled for, could be a potential confounder. Indeed, Domany et

al.[57] showed that adolescents with HSD/hEDS who were referred to a sleep clinic had a high rate of sleep disorders, such as sleep apnea and insomnia. Additionally, poor sleep has been associated with the development of chronic pain and can hinder effective pain treatment in adolescents[191, 193]. These findings underscore the importance of examining sleep health and sleep-related difficulties more thoroughly in adolescents with HSD/hEDS in order to develop effective treatment strategies that address the full spectrum of their symptoms.

Further, given the exploratory nature of Study IV, it is important to pursue additional confirmatory and replication research to better understand the interplay between pain, fatigue, psychological factors, and sleep health in this group.

Impact on physical activity

Balance is an essential prerequisite for physical activity, affecting both static and dynamic tasks[194, 195]. This is especially important for adolescents, as balance plays a key role in motor-skill development and social interaction, which are vital for overall physical and psychological well-being[196, 197]. The results from Study I revealed that the HSD/hEDS group performed statistically significantly worse on balance tests than the control group. To my knowledge, this was the first study investigating balance in adolescents with HSD/hEDS. Since it was performed, other studies investigating balance in adolescents with HSD/hEDS have been published, dealing with issues such as the wearing of foot orthotics[198] and the examination of postural control[199].

Balance difficulties may impact participation by adolescents with HSD/hEDS in physical activities. Although Study I did not specifically examine the relationship between balance and participation, it did demonstrate — using the Frequency of Participation Questionnaire — that adolescents with HSD/hEDS were more involved in sedentary activities such as non-sport games and less involved in sports and outdoor activities than their peers. The reduction observed in those adolescents' participation in sports and outdoor activities can affect their social lives. What is more, the adolescents in the HSD/hEDS group in Study I reported needing more frequent rest than their

healthy peers, which could limit their opportunities for social interaction, including after-school activities.

Research has shown that adolescents with *asymptomatic* hypermobility have similar motor skills, including balance, to their non-hypermobile peers[200, 201]. In adolescents with HSD/hEDS, by contrast, exercise-induced pain has been shown to be related to reduced aerobic fitness and physical capacity compared with a healthy control group[105]. It has been assumed that musculoskeletal pain leads to inactivity and deconditioning, resulting in poorer aerobic fitness[128]. Hence it can be speculated that the combination of joint hypermobility and pain may contribute to lower levels of physical activity and balance difficulties, which could explain the reduced participation in dynamic activities observed in adolescents with HSD/hEDS. In order to develop beneficial treatment strategies for adolescents with HSD/hEDS, more research is therefore needed to explore different types of training and physical activities that could improve joint stability, build muscle strength, and reduce pain.

According to the findings reported in this thesis, adolescents with HSD/hEDS tend to spend more time in sedentary activities and less time in moderate-to-vigorous physical activity than their healthy peers. Interestingly, however, neither group reached the recommended levels of physical activity for promoting health, which highlights a common concern about unhealthy living in all adolescents. Insufficient physical activity is indeed concerning, since it increases the risk of developing diseases such as cancer, cardiovascular conditions, and diabetes[18]. For this reason as well, it is crucial to develop sustainable interventions that encourage and maintain higher levels of physical activity over time.

However, to our knowledge, no study has yet investigated long-term interventions aimed at increasing levels of physical activity in adolescents with HSD/hEDS. Telford et al.[202] discusses the importance of having low-intensity physical activity replace sedentary movement behavior as an initial step toward increasing daily movement and facilitating higher-intensity physical activity in adolescents. Physiotherapy interventions generally have positive effects on pain[137, 138], which can facilitate participation in everyday

activities such as walking and cycling, thereby promoting physical activity in adolescents with HSD/hEDS.

As regards clinical practice, these findings suggest that regular physical activity, such as strength training, will still be beneficial for reducing pain in children with HSD/hEDS, as previous studies have shown[137, 138]. However, given the altered pain response to exercise observed in this population, it is important to develop tailored exercise protocols that take into consideration the unique pain experiences of individuals with HSD/hEDS. When designing treatment plans, clinicians should be aware of the possibility of central sensitization and a decreased hypoalgesic response to exercise.

Methods

Experimental pain measurement has proven useful in investigating and understanding generalized pain and central sensitization of pain in adult patients with chronic pain[91]. However, these methods are not as widely used in adolescents, which has been discussed as a disadvantage[186]. Within the framework of this thesis, Study II was conducted to ensure the feasibility of experimental pain measurements, as well as to test the data-collection process and explore how much time would be required. Based on the findings made in Study II, we decided to reduce both the measurements and the number of questionnaires in Studies III and IV.

We used a variety of questionnaires to capture the issues presented by adolescents with HSD/hEDS, such as fatigue, impaired functioning and participation, and factors that influence pain perception, such as anxiety, depression, and pain catastrophizing. Researchers must always strive to strike a balance between the demands placed on participants and the information needed to answer research questions. Given the delicacy of this tradeoff, it is not uncommon to realize in hindsight that certain data would have been valuable to include. In this case, for example, it might have been useful to add the Central Sensitization Inventory as a complement to the pain measurements[203] and to incorporate a more detailed categorization of pain occurrence in order to differentiate pain distribution better[204].

Physical activity was measured using an accelerometer which was attached to the participant's right thigh with medical tape. To reduce the risk of skin reactions, the edges of the accelerometer were rounded, and tape designed for sensitive skin was used. This placement was chosen to minimize the likelihood of participants forgetting to wear the device during the seven-day monitoring period. Some participants experienced minor skin reactions, while one reported a more significant reaction to the adhesive tape securing the accelerometer. These reactions may not be solely due to the tape but could also be attributable to factors such as heat and moisture buildup under the device. To reduce the risk of skin reactions in future studies, further modifications should be considered, including alternative placement or attachment methods.

Strengths and limitations

One of the principal strengths of Studies III and IV in this research project is their relatively large sample size, especially considering the limited research available on adolescents with HSD/hEDS. In fact, the sample of those studies is comparable in size to those of similar studies, which have included between 29 and 47 participants[82, 205, 206]. Another principal strength of the overall project is the novelty of its study focus. Study I was among the first to investigate balance and participation in adolescents with HSD/hEDS, while Study IV was among the first to assess physical activity in adolescents with HSD/hEDS using objective measurement techniques, such as the use of an accelerometer, which provide reliable data on physical-activity intensity and patterns.

When it comes to limitations, it must be pointed out that recruitment was a significant challenge, with only about one-third of the approached adolescents with HSD/hEDS agreeing to participate. The reasons for declining to participate are unknown, but it is possible that those individuals with HSD/hEDS who declined either did not identify with the research questions or felt too overwhelmed by their symptoms to participate in a study requiring additional healthcare engagement. The research questions were based on clinical experience and patient feedback. Nevertheless, there is a risk that we

may not have identified relevant research questions for the patient group, which may have contributed to the difficulties we experienced in recruiting participants.

Another possible limitation is that we may have missed potential participants. In clinical practice, it has proven difficult to diagnose HSD/hEDS within the Swedish healthcare system[7, 8, 207]. In Sweden, this diagnosis is supposed to be made by professionals in primary healthcare, but they often consider themselves to lack sufficient knowledge[8]. Hypermobility is sometimes used as a working hypothesis for unexplained chronic pain in adolescents. In some cases, hypermobility occurs in joints not assessed by the Beighton Scale. Then localized and peripheral HSD may be a good alternative to generalized HSD and hEDS. In practice, it appears that healthcare professionals tend to make the diagnosis not only based on the diagnostic criteria from 2017 but also on the frequency of comorbidities, which is not included in the diagnostic criteria. Moreover, a single diagnostic code for hypermobility syndrome is used for all types of hypermobility, including asymptomatic hypermobility and flat feet, with no link to HSD/hEDS. This makes it difficult to obtain a homogeneous group when selecting participants based on medical records.

Additionally, the diagnostic criteria have changed over the years. We made every effort to ensure the accuracy and reliability of the diagnoses within our study population. Hence the diagnostic criteria from 2017 were applied in Studies II, III, and IV[157]. Participants who no longer met the diagnostic criteria for either hEDS or HSD were excluded. This increased the homogeneity of the study groups and probably improved the representativeness of the results for the target patient population. Specifically, 12 of the 49 original participants in the HSD/hEDS group in Studies III and IV did not meet the 2017 diagnostic criteria for either hEDS or HSD. This highlights the clinical challenges involved in diagnosing these conditions based on symptoms alone. However, it may also have contributed to our difficulties in achieving the target sample size. Because of the potential limitations in terms of the inclusion of a sufficient number of patients meeting the criteria for HSD/hEDS, the results of this thesis should be interpreted with caution and may be generalizable to broader populations only to a limited extent.

Owing to the lack of available data regarding the population in question, the power calculations for Study III were based on data from Study II, which was a small feasibility study. Power calculations are recommended for determining a reasonable group size, but there is a risk of statistical relationships being misleading when such calculations are based on small study groups, which may affect the validity of a study[208, 209].

In terms of methodology, the participants were asked to refrain from taking analgesics for at least 24 hours before the pain measurements in Study III. This requirement may have led to selection bias, as it could have excluded participants with high pain levels. Since Study IV used the same population, this could have also influenced the results of Study IV. Additionally, there was a statistically significant age difference between the HSD/hEDS group and the control group in that population, although it was taken into account through adjustments in the analysis using a general linear model.

In Study III, an aerobic cycling test was used to achieve submaximal exercise, with the intensity of the exercise assessed with reference either to the attainment of a submaximal heart rate or to a self-rated Borg RPE of 15. While the Borg RPE is a widely used tool for assessing perceived exertion, it is inherently subjective. Previous research has indicated that intra-subject reliability between sessions is significantly better when a lactate-threshold protocol is used instead of subjective measures such as the Borg RPE[210]. However, we opted not to use a lactate-threshold protocol in this study. There thus remains a possibility that participants with lower levels of physical fitness might have reached their lactate threshold during the cycling test. However, if future studies were to consider using a lactate-threshold protocol, it would be essential to account for the potential challenges associated with implementing such a protocol. Specifically, a lactate-threshold protocol typically involves invasive procedures such as skin pricking to measure blood lactate levels[211], and this could represent an obstacle to participation both for adolescents with HSD/hEDS and for healthy adolescents. Furthermore, we did not assess whether the participants experienced any pain related to cycling on the day after the test, which could be considered in future studies.

Another potential limitation is the difficulty experienced in maintaining a completely pain-free control group. Approximately 25 percent of the members of the control groups reported some level of pain, albeit limited or occasional, whereas around 80 percent of the individuals in the HSD/hEDS groups experienced frequent or continuous pain. However, having a completely pain-free control group is hardly a realistic aim. This difference in the prevalence and severity of pain can in fact be said to reflect clinical reality reasonably well.

Finally, the exploratory nature of Study IV involved a focus on movement behavior, with no data being collected about other potentially relevant factors such as sleep quality, sleep difficulties, and cognitive/psychological aspects like anxiety and depression. Including these variables in a more comprehensive study design would yield a more robust understanding of the impact of physical activity on adolescents with HSD/hEDS. Additionally, the activity data collected were based on information about the participants in Study III, where one of the exclusion criteria was that the participants were not allowed to have played a sport at an elite level. Since no separate power analysis was specifically conducted for that part of the study, this may have influenced the results, particularly the low to moderate effect sizes observed regarding levels of physical activity.

Clinical implications

Clinical implications

The findings of this thesis suggest that clinicians should be aware of the following:

- Increased sensitivity to pressure and reduced pain inhibition after exercise may reflect changes in central pain mechanisms, such as central sensitization, extending beyond muscles and joints.

- Understanding central pain mechanisms is essential for developing effective treatment plans that address both the physical and psychological aspects of pain.

- Pain responses in individuals with HSD/hEDS may be altered, and therefore one needs to be aware of this during assessments and manual treatments, because such individuals may experience enhanced pain responses or discomfort even from light contact.

- A diminished pain-relieving response to physical activity may be present in individuals with HSD/hEDS, which could result in heightened pain following exercise.

- Regular physical activity, including strength training, could still offer benefits, although personalized exercise protocols are probably needed to accommodate the unique pain experiences of individuals with HSD/hEDS.

- Incorporating psychological strategies into physiotherapy may also enhance exercise participation in this population.

Conclusion

Conclusion

Based on four comprehensive studies, this thesis highlights the significant impact of pain on the daily lives of adolescents with HSD/hEDS, particularly in limiting their physical activity and participation. The presence of generalized pressure hyperalgesia and the limited exercise-induced hyperalgesia in the HSD/hEDS group may suggest central sensitization, indicating that treatment plans should address both central mechanisms and peripheral factors, thus recognizing the complex role of biopsychosocial influences. Additionally, adolescents with HSD/hEDS tend to be more sedentary and exhibit more sleep movements than their healthy peers. While no clear link was found between fatigue and movement during the day or during sleep, the findings highlight the importance of promoting physical activity and improving sleep health in this population.

While the research provides valuable insights, it also highlights the need for further studies, particularly long-term investigations into sustainable interventions that can improve physical activity and quality of life in adolescents with HSD/hEDS. Future research should focus on understanding the underlying mechanisms of pain and fatigue in this population and on developing comprehensive, targeted treatments that address the full spectrum of symptoms. These efforts should aim to reduce pain, enhance participation in physical activities, and develop effective health-promotion programs tailored to the adolescents' needs. Additionally, larger studies are required to validate the present findings.

Future perspectives

Future perspectives

As described in the introduction, HSD/hEDS has a clear impact on adolescents' daily lives. We have shown that these individuals, as a group, have low levels of physical activity and do not attain the amount of physical activity considered healthy according to official recommendations. Additionally, increased pain sensitivity has been observed, and the suspicion of central sensitization is strengthened by a reduced inhibitory effect of exercise.

Future research should progress from surveys and investigations to studies focused on treatment interventions with long-term follow-up. These studies should aim to provide a deeper understanding of pain management and increase levels of physical activity in adolescents with HSD/hEDS, potentially leading to improved treatment strategies, guidelines, and patient outcomes. Early interventions may help prevent or reduce the risk that these adolescents will develop central sensitization to pain. In the planning of these interventions, patients should play a crucial role in defining the content and outcome measures.

In relation to these findings, the following research questions would be worthy of further investigation:

Exercise-induced hypoalgesia (EIH): It would be valuable to conduct a subanalysis comparing the HSD/hEDS group experiencing widespread pain with a control group. If the former group´s EIH is also affected in the active muscle, the question arises whether their widespread pain is the cause of the reduced EIH and has become the primary pain issue that needs to be addressed, even if the initial cause was HSD/hEDS.

Clinical implementation: The incorporation of pain education and low-intensity physical activity into the standard treatment protocols for individuals with chronic pain conditions, particularly adolescents with HSD/hEDS, should be implemented in clinical practice and evaluated. Outcome measures could be changes in pain perception, functional ability, and psychological well-being as well as quality of life over time.

General pain and low-intensity exercise: The effects of low-intensity cycling on pain, pain catastrophizing, general activity levels, and sleep should be examined. Since a patient's attitude toward exercise is crucial for compliance, it may be valuable to explore whether individual characteristics influence outcomes.

Low-intensity exercise: The feasibility of low-intensity exercise as compared with more intensive physical activity in adolescents with widespread pain and HSD/hEDS should be tested. In this context, it should be determined what the appropriate duration and frequency of such exercise is. For example, a course of one term of training, 1–2 times per week, either in a group setting or individually, could be explored. The effects on pain, pain catastrophizing, activity levels, and sleep should be measured, and it should be assessed whether exercise-induced hypoalgesia can be evaluated.

I would also like to mention an additional research idea regarding diagnostic criteria:

Piezogenic papules: Are piezogenic papules (small, soft, skin-colored papules on the heels that can appear under pressure, which are included in diagnostic criterion 2(A) for hEDS) more frequent and more pronounced in adolescents with HSD/hEDS than in a healthy control group? Are these piezogenic papules perceived as painful? Is there a need for a clearer definition of when these papules are to be considered abnormal?

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Appendix

Appendix

Appendix 1: Classification of Ehlers–Danlos syndrome over time.

Former nomenclature (Berlin 1988) and other names	Villefranche 1997	International Classification 2017	Inheritance pattern*
EDS type I — Gravis EDS type II — Mitis	Classical type	**Classical EDS**	AD
		Classical-like EDS	AR
		Cardiac-valvular EDS	AR
EDS type IV — Arterial-ecchymotic	Vascular type	**Vascular EDS**	AD
EDS type III — Hypermobile	Hypermobility type	**Hypermobile EDS**	AD
EDS type VII a and b Arthrochalasis multiplex congenita	Arthrochalasia type	**Arthrochalasia EDS**	AD
EDS type VII c Human dermatosparaxis	Dermatosparaxis type	**Dermatosparaxis EDS**	AR
EDS type VI and VIa Ocular-Scoliotic	Kyphoscoliosis type	**Kyphoscoliotic EDS**	AR
		Brittle Cornea Syndrome	AR
EDS Progeroid	EDS progeroid type	**Spondylodyplastic EDS**	AR
EDS Kosho type; Adducted Thumb Clubfoot Syndrome	---	**Musculocontractural EDS**	AR
		Myopathic EDS	AD or AR
EDS type VIII	EDS periodontitis	**Peridontal EDS**	AD
EDS type IX Occipital Horn Syndrome	Menkes Syndrome	**---**	XR
EDS type X Fibronectin-deficient EDS	---	**---**	?
EDS type XI Familial Hypermobility Syndrome	---	**---**	AD
EDS type V — X-linked EDS	---	**---**	XR

* Inheritance patterns: AD = autosomal dominant; AR = autosomal recessive; XR = X-linked recessive[34].

Appendix 2: Flow diagram of participants for the HSD/hEDS groups in the different studies

	Study I Number	**Study II** Number	**Studies III and IV** Number
Enrollment Invited to participate	97	136	176
Excluded	22 failed to meet inclusion criteria. 14 moved away from the area. 41 declined or did not respond.	55 failed to meet inclusion criteria. 19 had no electronic medical records available. 5 moved away from the area. 44 declined or did not respond.	14 declined. 103 did not respond.
Allocation Agreed to participate	20	13	59
Excluded		1 failed to meet inclusion criteria. 1 failed to attend.	7 withdrew participation. 3 failed to attend.
Assessment	20	11	49
Excluded		1 declined to participate.	12 did not meet diagnostic criteria.
Analysis	20	10	37

Appendix 3: Flow diagram of participants for the control groups in the different studies

	Study I Number	**Study II** Number	**Study III** Number	**Study IV** Number
Enrollment Invited to participate	Unknown number information obtained through various channels.		Unknown number information obtained through various channels. 111 expressed interest and were invited to participate	
Excluded			20 declined. 35 did not respond.	
Allocation Agreed to participate	24	9	56	
Excluded			3 withdrew participation. 2 failed to attend.	
Assessment	24	9	51	
Excluded			2 showed signs of HSD. 2 had NRS pain >3 on the day of assessment.	2 showed signs of HSD. 2 had NRS pain >3 on the day of assessment. 2 lost the accelerometer. 1 interrupted the activity measurement.
Analysis	24		47	45