An exploration of the clinical characteristics and the impact of symptomatic hypermobility in children, adolescents, and their families

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Declaration

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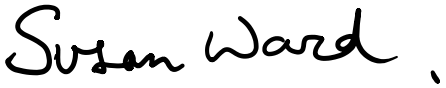

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List of Abbreviations

Abbreviation	Explanation
6MWD	Six-minute walk distance
6MWT	Six-minute walk test
ASHT	American Society of Hand Therapists
BJHS	Benign Joint Hypermobility Syndrome
BOT-2	Bruininks-Oseretsky Test of Motor Proficiency
BOT-2 Brief	Bruininks-Oseretsky Test of Motor Proficiency Brief
BS	Beighton score
BSPAR	British Society of Paediatric and Adolescent Rheumatology
CHI	Children's Health Ireland
CMAS	Childhood Myositis Assessment Scale
CSTAR	Centre for Support and Training and Analysis and Research
CYP	Children and young people
DPIA	Data Protection Impact Assessment
DTA	Data Transfer Agreements
EDS	Ehlers-Danlos syndrome
EDS-HT	Ehlers-Danlos syndrome hypermobility type
FPI	Foot Posture Index
GDPR	General Data Protection Regulation
HCTD	Heritable Connective Tissue Disorder
hEDS	hypermobile Ehlers-Danlos syndrome
HMS	Hypermobility Syndrome
HRQOL	Health Related Quality of Life
HSD	Hypermobility Spectrum Disorder
JH	Joint Hypermobility
JHS	Joint Hypermobility Syndrome
KEA	Knee Extension Angle
LLAS	Lower Limb Assessment Score

NCRC	National Children's Research Centre
OI	Osteogenesis Imperfecta
OLCHC	Our Lady's Children's Hospital
OSF	Open Science Framework
PAQ-C and A	Physical Activity Questionnaire - Child and Adolescent
pGALS	paediatric Gait Arms and Legs
PRISMA-ScR	Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
ScR	Scoping Review
TCD	Trinity College Dublin
WHO	World Health Organisation
YBT	Y-Balance Test

Abstract

Background: Children and adolescents with symptomatic hypermobility can present with chronic musculoskeletal pain and dysfunction, along with a wide variety of multi-systemic complaints. Clinical heterogeneity poses a challenge for healthcare professionals in diagnosis as well as determining appropriate care pathways, and the impact of symptoms on family life is not well understood. Overall this thesis aimed to explore, characterise, and classify symptomatic hypermobility as well as to assess its impact on children, adolescents, and their families.

Methods: This thesis employed a sequential mixed methods design. First, a scoping review was conducted using a developmental framework to determine the reported clinical characteristics of children and young people with symptomatic hypermobility. A cross-sectional study was then carried out on children and adolescents with symptomatic hypermobility. Cluster analysis was performed to identify potential subgroups of participants within this cohort. Following this, a qualitative semi-structured interview study was conducted, interviewing both patients and their families, using purposive sampling and reflexive thematic analysis. A staged approach was used to integrate the studies.

Results: Clinical characteristics were found to vary across developmental stages. Inconsistent diagnostic criteria and assessment methods were identified. Participants exhibited worse fatigue, function, strength, endurance, and motor skills compared to normative data. Three clinically meaningful subgroups were identified in this data reflecting different levels of proposed care needs: High Symptom Burden, Medium Symptom Burden, and Low Symptom Burden. Three themes were identified through qualitative interviews: 1) the need to make sense of symptoms, 2) the impact of symptoms on daily lives and 3) challenges in care pathways.

Conclusions: The identification of three clinically meaningful subgroups could lead to improved, targeted care pathways for symptomatic hypermobility. Greater clarity regarding clinical characteristics in symptomatic hypermobility could facilitate earlier recognition. The negative impact of symptoms on the participants and families' lives

highlights the need for a renewed focus on psychological and social determinants of health outcomes in symptomatic hypermobility.

Lay Abstract

Background: Joint hypermobility in patients is often seen in healthcare settings either as part of genetic conditions or associated with various symptoms. This research focused on symptomatic hypermobility, which isn't linked to a specific genetic cause. We need to better understand what symptomatic hypermobility means for children and their families. By categorising symptomatic hypermobility we could enhance patient outcomes and optimise healthcare resources by tailoring treatment to specific groups

Key Findings:

1. Clinical domains and developmental changes; symptomatic hypermobility affects different aspects of health and changes as children and adolescents grow. There is a lack of clear guidance on how to recognise hypermobility and related symptoms in clinical practice and research. Better study designs are needed to improve our understanding.
2. Identifying clinical characteristics and subgroups; we identified that those with symptomatic hypermobility had worse fatigue, quality of life, function, strength, endurance, and motor skills compared to children and adolescents of similar age and sex. Subsequently we identified three subgroups which could be used to target treatments. The groups were as follows:
    I. Low Symptom Burden
    II. Medium Symptom Burden
    III. High Symptom Burden
3. Themes from Lived Experiences; three themes emerged from interviews with children, adolescents, and their parents:
    I. The need to make sense of symptoms
    II. Symptoms shaped lives
    III. Challenges in the care pathway

Recommendations:

- Use standardised assessments in children and adolescents to recognise symptomatic hypermobility earlier
- Addressing musculoskeletal health in children could lessen socioeconomic costs in adulthood
- There is a need for better resources for patients, families, schools, and other healthcare providers to better understand symptoms
- Policy and behavioural changes are needed in school settings to help children and adolescents manage symptoms including pain and fatigue
- Better cohesion between healthcare services may reduce the impact of symptoms on families

In summary, understanding symptomatic hypermobility involves looking beyond the biological factors and considering social factors too. This could lead to better targeted care for affected individuals.

Value of Research

This research has identified that clinical characteristics in symptomatic hypermobility span many different clinical areas and change with developmental stages. This research provides greater clarity to assist in the earlier identification of symptomatic hypermobility. Early recognition is crucial for care and could help to reduce the socioeconomic burden of symptoms such as chronic pain into adulthood. Research gaps were identified, including the need for future longitudinal studies to explore the changing pattern of symptoms.

This thesis identified three subgroups of patients, named to reflect their proposed care needs which varied from Low to High Symptom Burden. Current waiting lists for tertiary services in Ireland are lengthy and participants presenting to a tertiary paediatric rheumatology service had significant levels of pain, fatigue, and poor quality of life, with reduced strength, function and motor skill proficiency compared to normative data. Earlier intervention is needed to prevent this significant symptom burden. If patients can be more effectively triaged in primary and secondary settings, this could help clinicians to better identify those requiring more intensive interventions in tertiary care. This could lead to a more established care pathways, with a better use of limited healthcare resources, with improved outcomes for patients.

One of the novel aspects of this thesis was the use of a sequential explanatory mixed methods design, which allowed data that was collected in the quantitative study to be analysed and inform the qualitative study. To date, clinical subgrouping has only been explored from a biomedical perspective. For the first time, this research found evidence that social factors and access to resources varied across subgroups and are key considerations in understanding the impact of symptoms. High levels of uncertainty, fear and worry about progression of symptoms were present. Social determinants of health were found to play a role in the experience of symptoms. Children, adolescents, and parents voiced the need for better resources and improved awareness in schools and healthcare settings. This thesis places the emphasis back on the patient's voice which should continue to be central to future research in this condition.

PhD Training and Outputs (August 2020 - March 2024)

Courses in Research Methodology

Post Graduate Certificate in Statistics	Year 1
Research Integrity and Impact in an Open Scholarship Era	Year 1
TCD webinars - Covidence, SPSS, Minitab, Endnote, Excel, Word, NVivo	Years 1-3
Academic writing workshops TCD Library	Year 1
Research Integrity Biomedical Sciences Epigeum Online Course	Year 1
An Introduction to Qualitative Research Methods for Health Research, Oxford University, 8-week online course	Year 3
Qualitative Research Methods Trinity College Dublin 2-days	Year 3

Conference Attendances

Irish Society of Chartered Physiotherapists Annual Conference	Year 1-3
EDS Summit, Online conference	Year 1
Paediatric Rheumatology European Congress	Year 1-3
International EDS Conference	Year 2
Irish Physical Activity Research Collaboration (iPARC) Symposium. Children and Adolescents in physical activity and sport.	Year 2
Irish Paediatric Orthopaedic Society	Year 2
World Physiotherapy Conference	Year 3
Children's Health Ireland Conferences 'Acute Journey and Beyond'	Year 3
Children's Health Ireland Conferences 'Essentials in JIA'	Year 3

Leadership and Management

Membership PRES Paediatric Rheumatology European Society	Year 2-ongoing
Membership BSR British Society of Rheumatology	Year 3-ongoing
Membership Chartered Physiotherapists in Paediatrics, Rheumatology and Research Clinical Interest Groups	Year 1-ongoing
Membership Irish Rheumatology Health Professionals Society	Year 1-ongoing
Membership Irish Physical Activity Research Collaboration (iPARC)	Year 3-ongoing
Workshop hypermobility screening recognition; skills and knowledge. CHI at Crumlin Rheumatology team.	Year 3
Workshop paediatric musculoskeletal assessment Children's Health Ireland Conference 'Acute Journey and Beyond'.	Year 3
Education Officer Rheumatology Clinical Interest group of the Irish Society Of Chartered Physiotherapists	Year 1-ongoing
Reviewer Irish Society of Chartered Physiotherapists Annual Conference	Year 3

Supervision and Lecturing

Principal Investigator 4th year student research project 'An investigation of the need for six practice trials for the Y-Balance Test in children	Year 1-3
Lecturing 2nd Year undergraduate musculoskeletal assessment skills	Year 1

Peer Reviewed Publications

- Ward S, MacDermott EJ, Simmonds J, Deane J, Mockler D and Dockrell S. 2022. Clinical characteristics of symptomatic hypermobility in children and young people: A scoping review protocol, Physiotherapy Practice and Research, 43, 63–69, DOI:10.3233/PPR-210601.
- Ward S, MacDermott EJ, Simmonds J, Deane J, Mockler D and Dockrell S. 2022. Symptomatic hypermobility in children and young people: A scoping review of clinical characteristics using a developmental framework, Physiotherapy Practice and Research, 43, 223–236, DOI:10.3233/PPR-220699.

Publications

- Protocol Registration to Open Science Framework. Submitted 20/09/21. Ward, S. McDermott, E. Deane, J. Simmonds, J. Mockler, D. Dockrell, S. Clinical characteristics of symptomatic hypermobility in children and young people: A scoping review. https://osf.io/m2h6q.

Presentations

Conference Presentations

- World Physiotherapy Congress 2023, Dubai. May 2023. SYMPTOMATIC HYPERMOBILITY IN CHILDREN AND YOUNG PEOPLE: A SCOPING REVIEW OF CLINICAL CHARACTERISTICS USING A DEVELOPMENTAL FRAMEWORK
- Children's Health Ireland Conference 'Acute Journey and Beyond'. May 2023. *Symptomatic Hypermobility in the Growing Child*
- Irish Orthopaedic Paediatric Society Annual Meeting, Dublin, November 2022. Paediatric Joint Hypermobility: an update from the Childhood Hypermobility Study.

- Irish Society of Chartered Physiotherapists, Annual Conference. October 2021. Clinical characteristics in children with symptomatic hypermobility: a scoping review protocol.

Other Presentations

- Irish Society of Chartered Physiotherapists, Chartered Physiotherapists in Rheumatology, AGM and Presentation. May 2022. *Joint Hypermobility in adults and children; an update for clinicians*
- Children's Health Ireland, Education for Allied Health Professionals. April 2022. *Symptomatic Hypermobility*
- Trinity College School of Medicine Faculty Research Blitz. April 2022. Trinity Biomedical Sciences Institute, Trinity College, Dublin. *Symptomatic Hypermobility in children and young people*
- Chartered Physiotherapists in Paediatrics, Irish Society of Chartered Physiotherapists. November 2020. *Hypermobility in Children and Young People. An update for clinicians.*
- CHI at Crumlin Rheumatology Team. January 2021. Development of a physiotherapy decision-making tool for paediatric joint hypermobility: a move towards targeted treatment. An introduction to the study, recruitment process and data collection.

Conference Abstracts

- European Paediatric Rheumatology Congress. 2023. Mapping clinical characteristics in children and adolescents with symptomatic hypermobility in tertiary paediatric rheumatology settings. An Irish perspective. Susan Ward, Sara Dockrell, Janet Deane, Jane Simmonds, Kelly Robinson, Edel Carberry, Clodagh Lowry, Orla G. Killeen, Nicola Ambrose, Emma J. MacDermott.
- Irish Society of Chartered Physiotherapists Annual Conference 2023. An Investigation of the Need for Six Practice Trials for the Y-Balance Test in Children Hannah Byrne Kennedy, Tara Dunne, Aisling Keller, Susan Ward, Sara Dockrell.

- Child Health Research Excellence Report Launch Conference. Trinity College Dublin. Paediatric Symptomatic Hypermobility: 2023. A Move Towards Targeted Care Pathways.
- Irish Society of Rheumatology Autumn Meeting. 2021. Abstract Symptomatic Hypermobility in children and young people: A Systematic Scoping Review.

Personal and Public Involvement

'News Rheum'. Quarterly newsletter co-produced by researchers and patients with rheumatic disease	Year 1
National Children's Research Centre Newsletter	Year 2 & 3
Collaboration with Irish Society of Chartered Physiotherapy; developing an infographic Scoping Review. Featured infographic of the month.	Year 3
Irish Rheumatology Health Professional Society Summer Newsletter. Hypermobility in Children and Young People.	Year 3
Article First Hand, e-zine (Irish Society Of Physiotherapy)	Year 3

Academic Collaboration

School of Medicine 'Meet the PhD researcher'	Year 1
Submission to 'Annual Overview of Doctoral Health Research 2022' Trinity College Dublin	Year 2
Submission to 'Trinity Child Health Brochure'	Year 3

Industry Collaboration

Children's Health Foundation (CHF): Short video production.	Year 3
National Children's Centre Annual Progress Reports 2020-2022 and 2022-2023	Year 1-3

Grants

National Children's Research Centre Clinical Fellowship Award. Development of a physiotherapy screening tool for paediatric joint hypermobility: A move towards targeted treatment. Grant Code. D/19/5. Start date 10.08.20.

Awards

World Physiotherapy Outstanding Platform Presentation award in respect of abstract SYMPTOMATIC HYPERMOBILITY IN CHILDREN AND YOUNG PEOPLE: A SCOPING REVIEW OF CLINICAL CHARACTERISTICS USING A DEVELOPMENTAL FRAMEWORK. Presented at World Physiotherapy Congress 2023.

Chapter 1 Introduction

1.1 Joint hypermobility

Joint hypermobility describes the ability of a joint to move beyond the typical range of motion (1). It is a physical trait that has been observed for centuries, as illustrated through the arts and humanities, and in ancient medicine when Hippocrates noted that the Scythians were unable to draw their bows because of joint hypermobility at their shoulders (2). However, it was not until the late 19th century when syndromes characterised by joint hypermobility, skin extensibility and tissue friability were first described (3). After this time Rheumatologists recognised a group of patients with joint hypermobility and rheumatological or orthopaedic symptoms where alternative diagnoses such as defined syndromes had been excluded (3). The association of joint hypermobility and symptoms outside of genetic syndromes can be seen as a 'spectrum'. The spectrum describes clinically relevant joint hypermobility which will be termed 'symptomatic hypermobility' and is the subject of this thesis (4, 5).

Since symptomatic hypermobility was first described, there has been ongoing debate about whether it is the upper end of a spectrum of normality or a common, mild hereditary disease of connective tissue. Whilst the latter has been proposed, any connective tissue abnormality or genetic defect is yet to be determined (6). This debate has been of particular interest in the field of paediatrics. Joint hypermobility is more common in children than adults and is commonly benign and present without any health-related manifestations (5, 7). Paediatric hypermobility becomes clinically relevant when it is associated with symptoms such as musculoskeletal pain (5). The spectrum of symptoms reported to be associated with hypermobility are also seen in other childhood conditions (8). Presentations are often chronic, clinically varied and aetiologically heterogenous (9, 10).

When assessing a child clinicians have to consider the impact of other physical and psychosocial factors which can present during growth and development within the social context of a family unit. Therefore, paediatric clinicians require a broad range of clinical examination skills, awareness of typical range of movement throughout childhood as well

as knowledge of other clinical conditions which may present with similar signs and symptoms.

1.2 Hypermobility and symptoms

A causal relationship between presenting symptoms and underlying hypermobility has been presumed (11) (Figure 1.1) but is not well understood. Presenting symptoms may be 'caused' by biomechanical and neuromuscular dysfunction resulting from existing or evolving joint instability in the presence of joint hypermobility (Figure 1.1) (11).

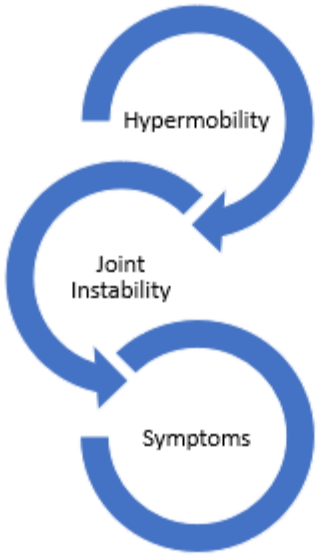


Figure 1.1 A proposed model for the causal link between hypermobility, joint instability, and musculoskeletal symptoms

However, a hypermobile joint is not always lax or unstable (12) yet episodes of joint pain are the most frequent symptom (13). Hypermobility is also associated with a growing number of symptoms involving other organs and tissues such as functional gastrointestinal disorders and cardiovascular dysautonomia (1). Wider connective tissue laxity or fragility affecting the structural integrity of connective tissue throughout the body has been proposed as a possible mechanism (14). A specific biological connection to tissue alterations is not clear and any biological markers are lacking (10).

1.3 Targeted care

Sláintecare is the ten-year programme to transform Ireland's health and social care services with a fundamental model summarised by their statement 'Right Care. Right Place. Right Time' (15). Sláintecare aims to ensure that the right treatments are provided to the right patient, which should take place locally if appropriate and that there is a reduction in unnecessary interventions (15).

Stratified care, or the matching of subgroups to patients with specific symptoms, is thought to be particularly appropriate for patients with heterogenous presentations (16, 17). Approaches such as the STarT Back tool are an example of a stratified tool used to target treatment in the management of adults with low back pain (16). Developing more targeted pathways aims to make best use of therapy resources, and direct care to where it is most needed.

Recognising paediatric hypermobility, excluding rare genetic disorders which present with hypermobility as a feature, and assessing and managing musculoskeletal and systemic symptomatology is a challenge (8, 18, 19). Clarity is needed to help paediatric clinicians to examine joint range with an awareness of typical movement and use recommended assessments in order to exclude other conditions with similar symptoms. Additionally, there is currently no guidance regarding whether one type of intervention is clearly better than another, or if there are subgroups of patients, that may benefit from interventions of varying levels of intensity (20, 21) (Figure 1.2)

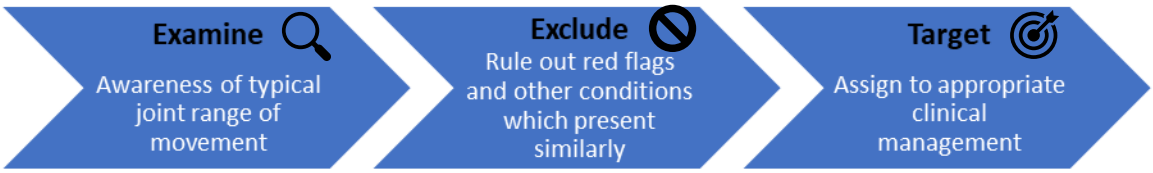


Figure 1.2 The challenge to recognition and management of paediatric hypermobility and symptoms

Given the lack of clarity in the understanding of what symptomatic hypermobility represents in a paediatric clinical cohort, there is a need to build on the existing literature and to address gaps in the research. This thesis sets out to explore the clinical characteristics of children and adolescents with symptomatic hypermobility, and to investigate if children and adolescents presenting with symptomatic hypermobility can be assigned to more homogenous clinical subgroups based on subjective and objective clinical measures. The impact of symptomatic hypermobility on family functioning is not clear and should be considered in the development of more targeted care pathways. Healthcare is complex, and a different approach was needed to answer the research questions posed in this thesis.

1.4 Study Design

A mixed methodology was chosen to capture not only the 'what' but the 'why', allowing us to examine not only objective clinical signs and symptoms, but also the subjective symptoms to develop an understanding of the experience of symptomatic hypermobility and the impact on family life. To answer the thesis research aims a sequential explanatory design was used. This involved the use of quantitative and qualitative data methodologies, and an integration or connection of both to understand the research problem (22). A sequential explanatory mixed-methods design was used where data were collected, analysed and connected consecutively in two phases: i) quantitively and ii) qualitatively (Figure 1.3) (23). Data collected at the quantitative stage informed the development of the interview topic guide used in the qualitative stage. The selection of participants for the interviews was a further point of integration; the quantitative study results provided the access to a subsample of children, adolescents, and their parents for the qualitative interviews. The selection of specific children and adolescents and their parents from three identified clinical subgroups allowed for exploration of the impact of varying levels of symptoms on children, adolescents, and their families. Integrating the lived experience provided further insight and information on other factors that influence the impact of symptoms from the perspective of the child, adolescents, and their parents.

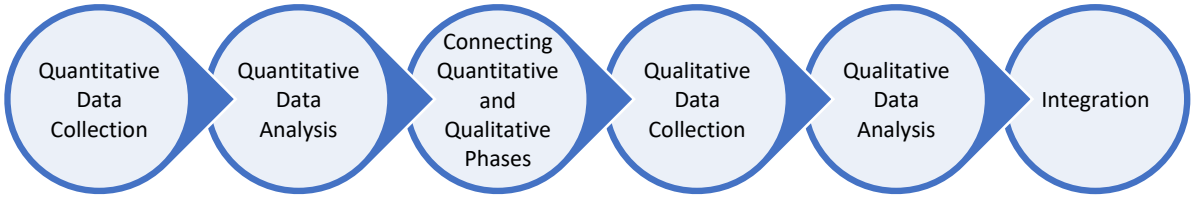


Figure 1.3 Summary of sequential mixed methods research design and phases (23)

In addition to study reporting guidelines for each study (24-26), the guidelines for Good Reporting of A Mixed Methods Study were also used to assist the transparency of overall reporting (Table 1.1) (27).

Table 1.1 Good Reporting of A Mixed Methods Study. Adapted from O'Cathain et al., 2008 (27)

1.	Describe the justification for using a mixed methods approach to the research question
2.	Describe the design in terms of the purpose, priority, and sequence of methods
3.	Describe each method in terms of sampling, data collection and analysis
4.	Describe where integration has occurred, how it has occurred and who has participated in it
5.	Describe any limitation of one method associated with the presence of the other method
6.	Describe any insights gained from mixing or integrating methods

1.5 My background

As a paediatric physiotherapist, my own professional clinical experience and research has been spent working nationally, and internationally with children, adolescents and young adults in rheumatology, and sports medicine settings in Ireland, Scotland, and New Zealand. In the past 17 years, my work has been more focused on the management of children and adolescents with inflammatory and non-inflammatory conditions including symptomatic hypermobility, presenting to tertiary paediatric rheumatology settings in Ireland. This thesis has been strongly influenced by my clinical perspectives.

1.6 Biopsychosocial model

Exploring paediatric hypermobility and symptoms within a purely biomedical model lacks insight into the impact on health and disability within family life. The biopsychosocial model was used in this thesis to look beyond the focus of the biomedical model. This model is particularly helpful in chronic presentations (28). The model, proposed by Engel in 1977 (29), hoped to expand the biomedical approach to acknowledge biological, psychological and social influences in healthcare.

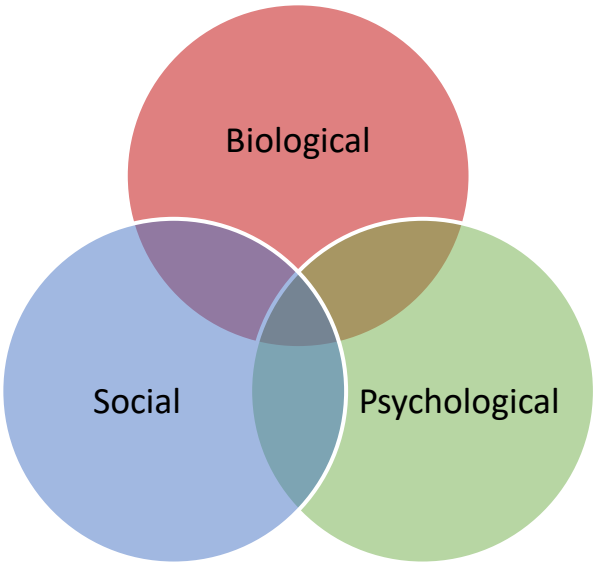


Figure 1.4 The Biopsychosocial Model. Adapted from Engel et al., 1977 (29)

Disability and health conditions occurring in children and adolescents are different to adults, in their nature, intensity and impact (30), and recognising the role of family functioning and school environment is key. Understanding the role of the social environment and the interaction with both biological and psychological health, has been explored in advancing the understanding of pain (31). This aspect of the biopsychosocial model is relatively unexplored within physiotherapy, but developing and evaluating interventions to target social factors could be an innovation where physiotherapists could play a large role (31). This is particularly important in paediatrics, where the functioning

of a child cannot be assessed in isolation, without consideration of their interaction with their family, peers, and their social environment including school.

It has been proposed that the biopsychosocial model may oversimplify clinical presentations into three fragmented areas of 'bio', 'psycho' and 'social'. This could result in a reductionist approach, lacking an understanding of how these three areas interact (28). A review of literature on low back pain assessment and management where the model is widely used, found that clinicians were more focused on biomedical or behavioural factors and that this may lead to clinicians forgetting the social connection to the world around them (28).

The use of a sequential explanatory mixed-methods design where data was collected analysed and connected consecutively, provides further integration beyond the biological or biomedical impacts of symptomatic hypermobility to address the social dimensions of symptomatic hypermobility, exploring how children and adolescents with symptomatic hypermobility function in social environments, including family life at home, life at school, and interactions with peers. This integration will help to avoid the potentially, reductionist approach offered by the biopsychosocial model by forming connections between different components (28) (Figure 1.4).

1.7 Growth and development

Any assessment and subsequent interpretation of clinical findings has to be viewed in the context of growth, development, and maturation, with knowledge of typical development, and conditions specific to different stages of growth and development (18).

Each study of this thesis was designed to be viewed through a developmental lens, where the impact of growth and development of the child was a key factor. Children and adolescents are not 'small adults', the pathway from birth to adulthood is recognised by growth, development and maturation (32). During this time, significant changes occur biologically, socially and in the psychological characteristics of an individual (30). Growth is the most significant biological activity during the first 20 years of life, with the timing and tempo differing significantly between systems, and between individuals (32). The

physical changes that occur during maturation can sometimes lead to increased susceptibility to injury, or growth-related pathology (33).

Defining the phases of life has changed over the years (34). The UN convention on the Rights of the Child defines a child from 0-18 years, and adolescence overlapping this period, from 10-19 years (35). Similarly, the World Health Organisation defines adolescence from 10 to 19 years (36). An expanded definition of adolescence is now recognised that aligns with adolescent growth which is known to extend into the 20's, with major social-role transitions (34). Recently, researchers working in the area of paediatric pain, have implored clinicians and researchers to use consistent language in the definitions of adolescence in particular, to ensure greater clarity and consistency (37).

Throughout the thesis, the need for consistent language was taken into consideration alongside the practicality of the current landscape. Of particular importance, the scoping review in Study I uses the following definitions to describe the age stages: childhood 0-9 years, adolescence 10-19 years and young adults 20-24 years (38). Study I recognises the extended age range of adolescence which explores the literature from birth to 24 years of age. However, the term '*young adult*' was used, reflecting research where subjects in the age group 20-24-years were reported in adult studies. In Study II and Study III, children and adolescents aged between 6 and 16 years were recruited, therefore the term '*child*' was used for those aged 6 to 9 years and '*adolescent*' used for those aged 10 and over.

1.8 Aims of the thesis

The overall aim of this thesis was to investigate, characterise and classify paediatric symptomatic hypermobility as well to assess its impact on children, adolescents, and their families. The outline of the three studies and specific aims of each study of the thesis are described in Figure 1.5. The first aim was to systematically explore and summarise the literature reporting symptomatic hypermobility in children, adolescents, and young adults, using a developmental framework which is carried out in Study I, Chapter 3. The clinical characteristics of children and adolescents have previously been determined in other cohorts; however, this has not been conducted in an Irish setting. Study II, Chapter

4 has two aims. The primary aim was to explore the clinical profile of children and adolescents presenting with symptomatic hypermobility in a paediatric rheumatology setting in Ireland. The secondary aim was to determine whether clinical subgroups can be identified. The impact of symptomatic hypermobility on family functioning is unclear. Study III, Chapter 5 of this thesis aims to explore the impact of symptomatic hypermobility on the lives of children, adolescents, and their families (Figure 1.5).

1.9 Outline of the thesis

Chapter 1. Introduction

An introduction to the subject matter of this thesis is described, along with the key considerations common to each study. The aims of the thesis are declared.

Chapter 2. Joint Hypermobility

The topic of hypermobility is presented in greater detail. The full continuum of hypermobility is explored. The spectrum bridging asymptomatic hypermobility to more syndromic forms of hypermobility is described, including terminology, assessment tools, differential diagnoses, associated comorbidities and management.

Chapter 3. Systematic scoping review

Chapter 3 is the first of the three exploratory studies in this thesis. This study, Study I, is a scoping review of the literature exploring the clinical characteristics of children, adolescents and young adults with symptomatic hypermobility using a developmental framework.

Chapter 4. Quantitative cross-sectional study

Study II is presented in Chapter 4. This is a quantitative cross-sectional study mapping the clinical characteristics of children and adolescents aged 6-16 years presenting to a tertiary paediatric rheumatology setting in Ireland. Clinical characteristics were identified, using standardised, valid, and reliable assessments to explore the wide range of symptoms from childhood to adolescence. Data were also collected from patient medical records and a structured interview, to explore other variables such as musculoskeletal and extra-

articular clinical presentations, additional diagnoses, time to diagnosis, school attendance and ethnicity. Cluster analysis was then used to determine if clinical subgroups or distinct clinical phenotypes could be found. As the time period of Study II took place during the Covid-19 pandemic and also at the time of the HSE-Cyber Attack (39), the impact of these significant events is considered and discussed at the end of Chapter 4.

Chapter 5. Qualitative interview study

Chapter 5 presents the final study in this thesis, Study III, a qualitative study that explored the lived experience of the impact of symptomatic hypermobility in children, adolescents, and their families. This study used reflexive, thematic analysis to explore the impact of symptoms in a more in-depth manner, in particular the social and environmental impacts on peers, schooling, parental occupation and activities.

Chapter 6. Discussion and Conclusions

Finally, in Chapter 6 the overall findings for each study are reviewed, and the integration and critical analysis of the key findings from each study is undertaken. The final section presents recommendations for future research and conclusions.

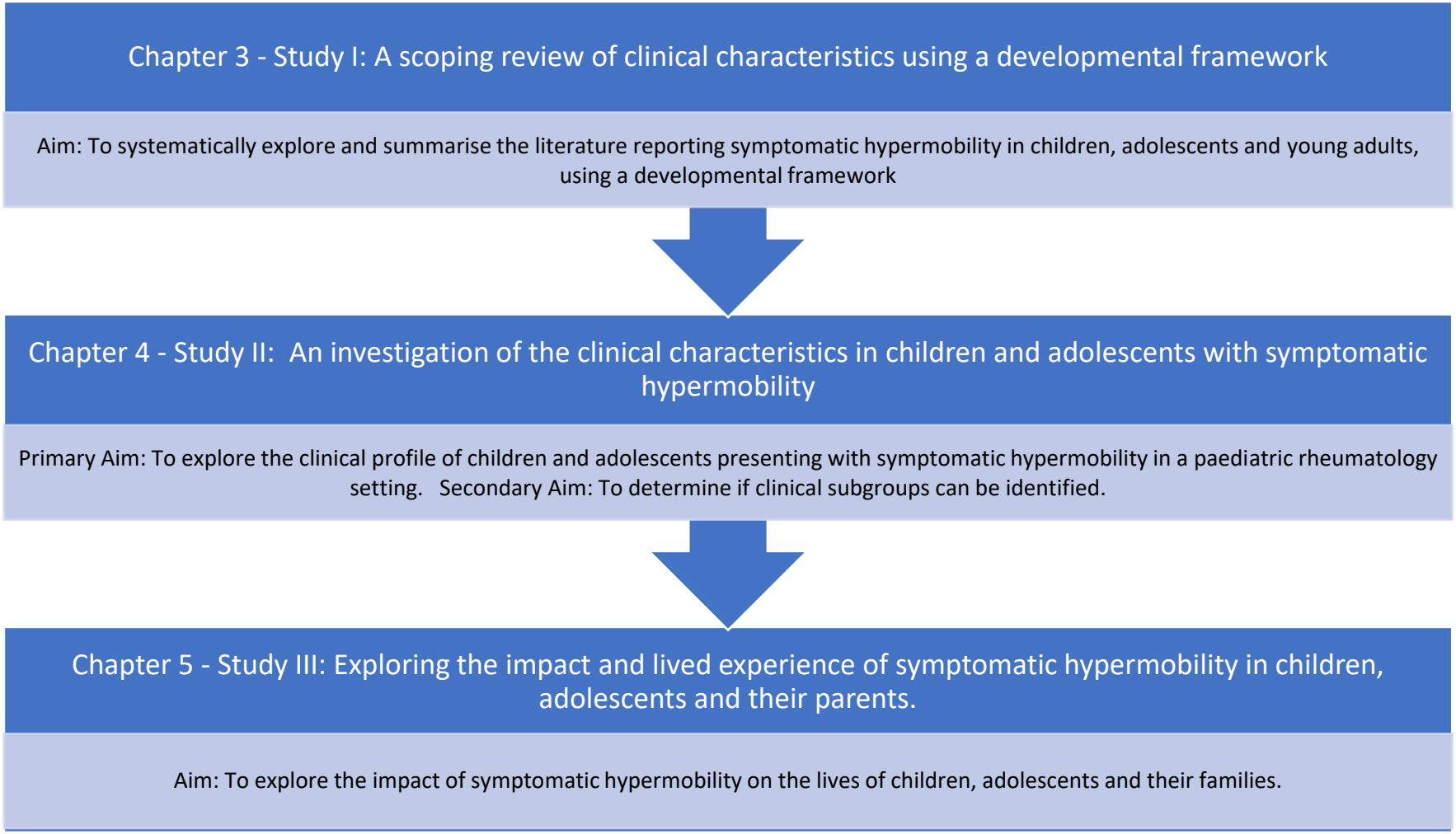


Figure 1.5 Thesis studies and aims

Chapter 2 Paediatric Hypermobility

2.1 Background

Joint mobility is a physical trait, continuous in nature, with variation thought to begin *in utero,* influenced by both genetic and environmental factors (12, 40). Joint mobility is impacted by age, sex, and ethnicity (7, 40). Joint *hyper*mobility herewith known as *hypermobility* is a descriptive term, referring to the ability of a joint to move actively or passively beyond its normal range of movement along its physiological axis (11, 41). Other terms that have been used include 'joint laxity', 'double-jointed', or 'loose' joints (12). Some confusion can arise when these terms are used interchangeably; some joints can be hypermobile but not lax or unstable (12). Hypermobility is not a diagnosis and has recently been described as a clinically neutral term (19).

2.2 Historical references to hypermobility

References to hypermobility appeared as early as the 4th century, in the arts, humanities and ancient medical texts (42). It was widely understood that the virtuoso violinist Paganini had significant flexibility in his fingers which was perceived to be of benefit to his playing (2) (Figure 2.1). The earliest publications of cases describing laxity of ligaments and skin hyperextensibility were by dermatologists, Tchernabogov in Russia (1891), Ehlers in Denmark (1898), and Danlos in Paris (1908) (43). In the 1930's, a physician in London, Parkes Weber, termed the disease Ehlers-Danlos syndrome to recognise the syndromic presentation of joint hypermobility along with skin hyperextensibility, abnormal scar formation and easy bruising (44).

Figure 2.1 Paintings of Paganini's hypermobile hands and fingers by Ludwig Burmesister, also called Lyser. Source: Pedrazzini et al., 2015 (45)

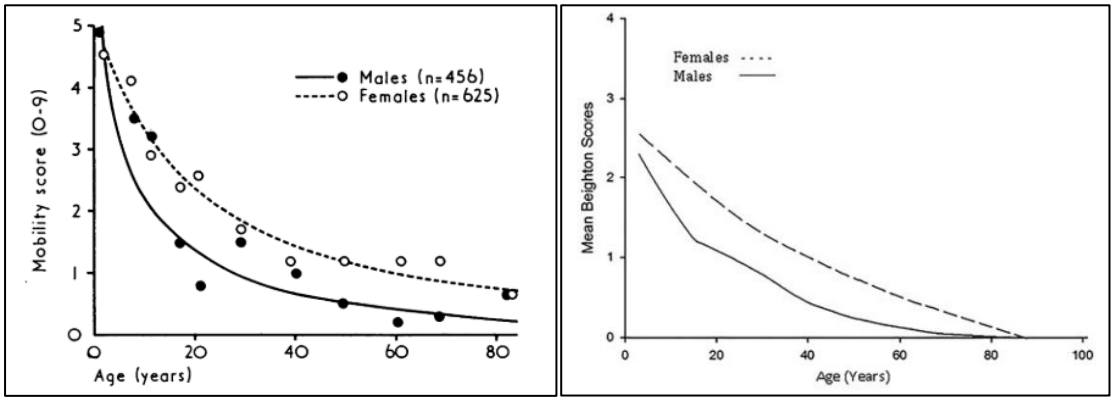
2.3 Classifying hypermobility

Hypermobility can be classified in terms of location and how widespread it is (11). When hypermobility can be localised to one or a few joints, this term is called localised joint hypermobility (LJH). Localised hypermobility can be inherited or an acquired trait such as following a previous trauma, or the result of training (spinal hypermobility) (41). Joint hypermobility which is observed at multiple sites, specific to hands and feet, is called peripheral joint hypermobility (PJH) (19). Where hypermobility is present at multiple sites, involving the 4 limbs and the axial skeleton, the term generalised joint hypermobility (GJH) can be used (41).

2.4 Prevalence of hypermobility

Hypermobility is common in children and adolescents (7). Beighton et al., 1973 confirmed this, and found that hypermobility was not only more common in younger children but also in females, when measuring the joint ranges in 1081 adults and children in a population survey of villagers living north of Johannesburg in South Africa (46). A more recent population study examining generalised joint hypermobility in 1,000 individuals

aged 3-101 years in Australia also found that generalised hypermobility was significantly influenced by age, sex and ethnicity (47). Figure 2.2 compares the relationships between joint mobility, age and sex across two populations in South Africa and Australia, with higher scores evident in the South African population (46, 47).



a **b**

Figure 2.2 Relationship between joint mobility, age, and sex in African (46) (a) and Australian (47) (b) populations.

More specifically in children and young people, a recent systematic review found the global prevalence of joint hypermobility in children and adolescents to be 34.1% but reported a range between 3.3% (12–13-year-old boys in Denmark) to 65% (overall prevalence of children aged 3-13 years in Hong-Kong) (48). The prevalence of generalised hypermobility was observed in 28% of girls, and 14.6% in boys in an Irish study of children aged 6-12 years referred to a community paediatric physiotherapy service (n=32) and a local primary school (n=41) (49). A UK study looking at a larger population-based cohort of 14-year-olds (n=6022) reported a prevalence of hypermobility of 27.5% in girls and 10.6% in boys (50). The wide range of reported prevalence is indicative of the heterogeneity of the studies carried out using different populations, methodologies, and most notably the definition and evaluation of hypermobility (48).

2.5 Measurements of hypermobility

Establishing hypermobility in any joint requires the use of the right measurement tools (19). Joint range of motion can be measured using a universal goniometer, a simple device which is lined up against specified bony landmarks, proximal and distal to the joint being evaluated (Figure 2.3) (51). Joint ranges measured with a universal goniometer are reported in degrees. This indicates a graded phenomenon, or a continuous variable. Within the general population, hypermobility should be attributed to a joint whose maximal range represents +2 standard deviations from the mean, falling above the 95th centile (19).

Goniometry is a valuable tool for assessing individual joints, and electric goniometers are now available which are reliable and feasible to use in both clinical and research settings (52).

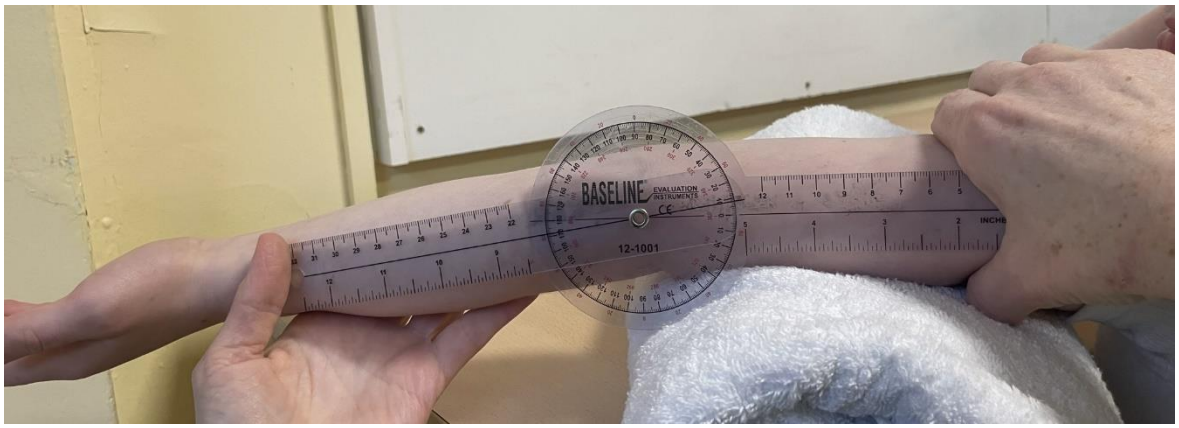


Figure 2.3 Joint range of motion measured using a universal goniometer

However, determining hypermobility has not been limited to measuring degrees of joint range. Many other clinical assessment methods have been described to assess hypermobility (53). A systematic review described the properties of six clinical assessment methods, excluding tests which authors deemed to have more advanced clinical methods (53). Four clinical tests; Beighton score (BS), Carter and Wilkinson, Hospital del Mar and Rotes-Querol and two questionnaire assessment methods; 5-point questionnaires and Beighton score self-reported, were identified (53). The reliability and validity of the included tests were evaluated from collected studies (n=33) reporting their

measurement properties (53). Most of the studies used the Beighton score, and it was deemed acceptable to use in clinical practice (53). The three other clinical tests lacked reliability and validity and the questionnaire methods had only been used in adult studies (53).

2.5.1 Beighton score

The Beighton score (BS) is the most commonly used tool to screen for generalised hypermobility (53). The BS was originally designed to be an epidemiological screening tool for GJH used in a South African population (46). The BS is made up of five movements. Four manoeuvres are tested on both sides of the body (bilateral thumb opposition to the flexor side of the forearm, fifth metacarpophalangeal extension, elbow extension, and knee extension) (Figure 2.4).

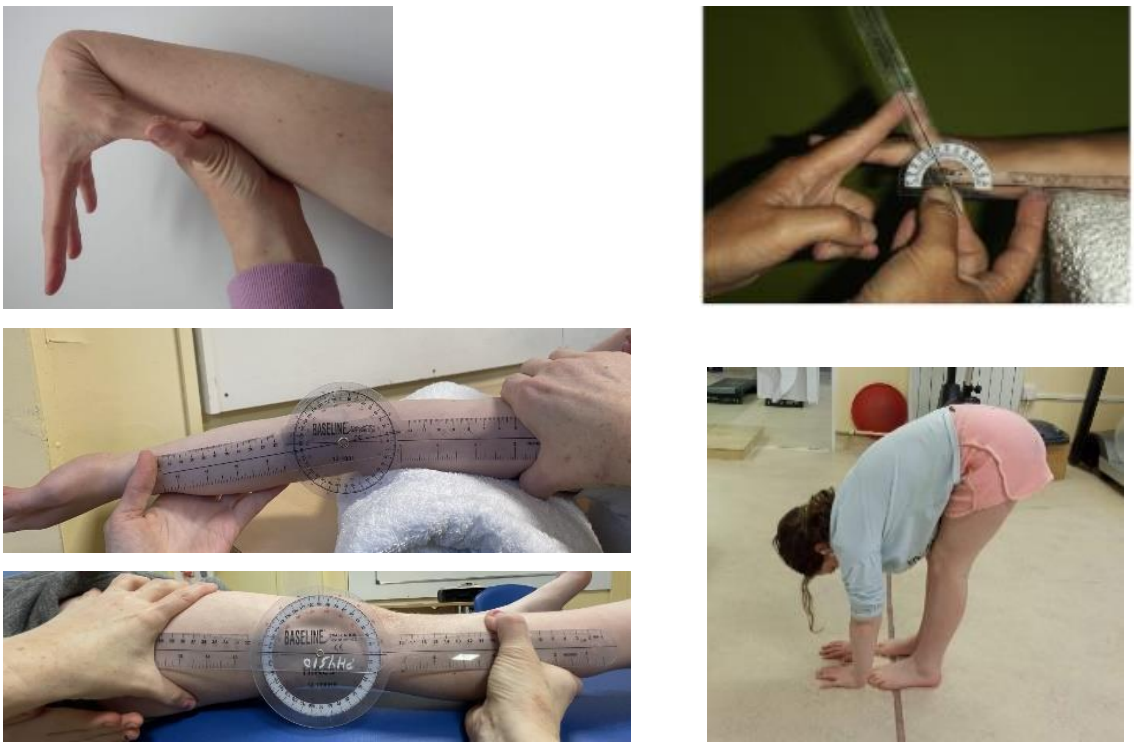


Figure 2.4 The five movements used in the 9-point Beighton score (54)

The fifth test is the ability to place both palms on the floor while standing with the knees straight (Figure 2.4) (54). One point is scored for each positive test, giving a maximum score of nine-points (Table 2.1) (54). Historically, the cut-off points for the BS have been variable (55). The consideration of two cut-off points in children which depend on the individual growth periods were considered, with a cut-off point of at least 6/9 recommended (53).

Table 2.1 The 9-Point Beighton score

Description	**Bilateral Testing**	**Scoring (maximum points)**
Passive dorsiflexion of the fifth metacarpophalangeal joint to ≥ 90 degrees	Yes	2
Passive hyperextension of the elbow ≥ 10 degrees	Yes	2
Passive hyperextension of the knee ≥ 10 degrees	Yes	2
Passive apposition of the thumb to the flexor side of the forearm, while shoulder is flexed 90 degrees, elbow is extended, and hand is pronated	Yes	2
Forward flexion of the trunk, with the knees straight, so that the hand palms rest easily on the floor	No	1
TOTAL		**9**

Adapted from Smits-Engelsman et al. 2011 (54)

2.5.2 Lower Limb Assessment Score

Two other tools have been described, using more advanced clinical methods, which assess multidirectional joint hypermobility (56). The Lower Limb Assessment Score (LLAS) was developed to assess hypermobility in the lower limb in children, excluded in the above review due to its advanced assessment methods (56). The tool consists of the assessment of 12 movements of the lower limb joints in several planes of motion and includes movements which would be used by clinicians working in musculoskeletal assessment such as physiotherapists, rheumatologists, and podiatrists who were involved

in its development (56). A score of ≥7/12 was agreed as a threshold for hypermobility in children (56), and in adults (57).

The Upper Limb Hypermobility Assessment Tool (ULHAT) was developed more recently and tests the mobility of upper limb joints in multiple planes of motion (58). Like the LLAS, the ULHAT also encompasses assessment of joint instability and the planes in which instability can frequently occur, which can be helpful for clinical decision making (58). However, the ULHAT has yet to be validated in children (58).

2.6 Reliability and validity of hypermobility measurements

The reliability and validity of methods used to assess hypermobility are inconsistent (53). Factors such as standardised positions of testing, or the inclusion of a warm-up period prior to the test may influence the outcome of the test (53). Some measures lack information regarding their reliability and validity (53). The questionnaire methods are only reported in studies of adults and also lack information regarding reliability and validity (53).

Two studies have described the intrarater reliability for the Beighton score (53). Only one of these studies was conducted in children (n=50) who had asymptomatic hypermobility (defined as ≥7/9 BS) (59). Criteria for eligibility were limited ('school children'), examiners were not blind to testing, and the method was not well described (59). Six studies have described the inter-rater reliability for the Beighton score (53). Three studies were conducted in children (59-61), but only two described the whole test (59, 61). Junge et al., 2013 compared two methods of carrying out the Beighton score in healthy school children aged 7-8 and 10-12 years, classifying GJH defined as cut-off ≥5/9 (61). Starting positions, and whether the joint was moved actively or passively were varied (61). The BS has been shown to be valid, when determining GJH in 500 Caucasian children aged 6-12 years (54). Children who scored high on the BS (BS >5/9) also showed increased range of motion in eight different joints (54). Whilst authors felt that further studies were required, in particular regarding validity, the BS was considered the most acceptable tool,

for classifying generalised hypermobility, once testing procedures are standardised, and recommended cut-offs are used (53).

The Lower Limb Assessment Scale has been found to be valid and reliable in both children (62) and adults (57). However the tool uses more advanced assessment methods, and further studies are required to test validity and reliability in different settings.

2.7 Other genetic conditions associated with hypermobility

The presence of hypermobility may also be a feature of an underlying genetic disorder (11). Several Heritable Connective Tissue Disorders (HCTD), which includes Marfan syndrome, some types of Osteogenesis Imperfecta (OI), Loeys-Dietz Syndrome, Stickler syndrome and Ehlers-Danlos syndromes (EDS) commonly present with hypermobility (Figure 2.6) (11). Hypermobility may also be a feature of skeletal dysplasias, hereditary myopathies and chromosomal disorders (11) (Table 2.2). For most, genetic testing is available to confirm a number of these recognised syndromes, and strict clinical criteria are used to diagnose Marfan syndrome, specific types of EDS and OI.

Table 2.2 Genetic conditions featuring hypermobility

Condition
Hereditary Connective Tissue Disorders (Ehlers-Danlos syndromes and related disorders, Marfan syndrome, Beals syndrome, Loeys-Dietz syndromes, Shprinzen-Goldberg syndrome, Hereditary cutis laxae)
Skeletal Dysplasias
Hereditary myopathies
Chromosomal and genetic disorders (such as Trisomy 21)
Multiple congenital anomalies/intellectual disability disorders

Adapted from Castori et al., 2017 (11)

The Ehlers-Danlos syndromes are a group of heritable conditions, which are heterogenous in presentation, but share clinical features including joint hypermobility, soft and hyperextensible skin, abnormal wound healing, and a tendency to bruise easily (10). Their classification has changed over time, the most recent classification in 2017

identified 13 variants, presented in Table 2.3, most of which can be determined by genetic testing (10). The one exception is the hypermobile EDS (hEDS) type which has no identifiable genetic cause (10). There is currently an international project with an aim to identify potential biomarkers for hEDS (hypermobile Ehlers-Danlos syndrome Genetic Evaluation HEDGE study), but this work is still ongoing (63). Some authors speculate that it is more complex, and that phenotypes are affected by multiple internal and external factors, which not only include genetic, but also, developmental, functional and environmental (1).

Table 2.3 Classification of the Ehlers-Danlos syndrome

EDS Type	Inheritance and Gene(s)	Hypermobility	Skin features	Other clinical features
Classical EDS	AD COL5A1, COL5A2, Rare: COL1A1	Generalised	Stretchy, doughy, fragile, atrophic scars	COL1A1 may present with osteoporosis and arterial aneurysms
Classical-like EDS	AR, TNXB	Generalised	Stretchy, velvety, no atrophic scars	Foot deformities, muscle weakness/atrophy
Cardiac-valvular EDS	AR, COL1A2	Gen. or peripheral	Stretchy, fragile, atrophic scars	Progressive cardiac valve abnormalities
Vascular EDS	AD, COL3A1, Rare: COL1A1	Peripheral	Translucent, fragile, atrophic scars	Arterial or intestinal rupture; uterine rupture' carotid – cavernous sinus fistula
Hypermobile EDS	AD, unknown	Generalised	Mild; soft, stretchy, atrophic scars	
Arthrochalasia EDS	AD, COL1A1, COL1A2	Generalised (severe)	Stretchy, fragile, atrophic scars	Hypotonia
Dermatosporaxis EDS	AR, ADAMTS2	Generalised	Stretchy, doughy, extreme fragility, atrophic scars	Characteristic facial feature; growth retardation; short limbs; bladder or diaphragm rupture

Kyposcoliotic EDS	AR, PLOD1, FKBP14	Generalised	Stretchy and fragile	Hypotonia; arterial rupture; early onset kyphoscoliosis
Brittle-Cornea syndrome (BCS)	AR, ZNF469, PRDM5	Peripheral	Soft, velvety, translucent	Thin cornea; blue sclera; hearing loss
Spondylodysplastic EDS	AR, B4GALT7, B3GALT6, SLC39A13	Generalised or peripheral	Stretchy, doughy, translucent	Short stature; hypotonia; bowing of long bones; developmental delay
Muculocontractual EDS	AR, CHST14, DSE	Multiple contractures; recurrent dislocations	Stretchy, fragile, atrophic scars, palmar wrinkling,	Characteristic facial features; large hematomas
Myopathic EDS	AD or AR, COL12A1	Peripheral; proximal contractures	Doughy, atrophic scars	Hypotonia; developmental delay
Periodontal EDS	AD, CR1, C1S	Peripheral	Stretchy, fragile, atrophic scars	Severe periodontal disease; frequent infections

Hypermobile EDS (hEDS) identified in red. Adapted from Tinkle et al., 2020 see Malfait et al. 2020 for full details of EDS classification (10, 12). AD: autosomal dominant; AR: autosomal recessive; Inheritance and Gene (encoded protein)

2.8 Hypermobility and musculoskeletal complaints

The association of hypermobility with complaints of a musculoskeletal nature was first described in the literature about 6 decades ago (64). In children and adolescents with hypermobility and symptoms, musculoskeletal manifestations are frequently the most common complaint (19). Hypermobility (≥6/9 BS) may represent a risk factor for the development of musculoskeletal pain in adolescence, particularly shoulder, knee and ankle pain. There is some evidence that higher pain scores were observed in those with hypermobility and risk of knee pain in adolescents with hypermobility was particular high in those who were obese (65). The mechanisms underlying the development of symptoms, are not well understood, but one theory is that the presence or development of joint instability, could be a factor influencing the onset of symptoms (11).

2.9 Hypermobility and non-musculoskeletal complaints

The association of hypermobility with non-musculoskeletal features and symptoms is proposed to be due to structural anomalies in skin, vessels, bone, muscles, and the nervous system (19). Children with symptomatic hypermobility had higher skin extensibility, a significant increase in collagen degradation products in urine, significantly decreased ultrasound measurements in bone indicating lower bone density, and a lower diastolic blood pressure, than children with asymptomatic hypermobility in one study (66). Authors concluded that results may be explained by variation in connective tissue composition in such individuals (66). In the presence of multi system complaints, determining whether hypermobility is clinically relevant, and part of a pathological or physiological process is difficult and controversial (8, 19).

2.10 Paediatric conditions presenting with similar symptoms

Children and adolescents are not ‘mini adults’ and aspects of growth and development are necessary to be considered in determining the clinical relevance of hypermobility in the presence of symptoms (18). Musculoskeletal symptoms are commonly associated with hypermobility (19), however, musculoskeletal complaints in children and

adolescents are common (18). Symptoms such as fatigue, abdominal pain and back pain are also common in adolescence, with almost 8% reporting daily headaches, 10% daily back pain and 16% sleepiness in the morning (67). Pain in childhood is different to pain in adults for many reasons including differences in physiology, cognition, developmental changes, and psychosocial reasons (68). Complaints may represent increasing educational, social, and sporting demands in the context of rapid growth and sexual development (67). Conditions such as paediatric chronic pain are often associated with other symptoms and comorbidities such as dysautonomia and fatigue (6). Where hypermobility co-exists with such heterogenous symptoms, determining the clinical relevance of paediatric symptomology is not straight forward (69).

2.11 Classifying clinical phenotypes

Castori 2020, proposed five classes of clinical phenotypes with hypermobility (19). A systematic process is detailed, which classifies an individual presenting with hypermobility. Castori 2020, stressed that the clinician must examine hypermobility in the context of the clinical presentation, with a full system exam and investigations as appropriate (19).

Table 2.4 Proposed five classes of clinical phenotypes with hypermobility (19)

Class 1:	Non-syndromic asymptomatic hypermobility
Class 2:	Non-syndromic hypermobility with musculoskeletal manifestations and/or related comorbidities
Class 3:	Non-syndromic hypermobility unrelated to the clinical problem
Class 4:	Syndromic hypermobility within recognizable genetic disorders
Class 5:	Hypermobility within unrecognizable syndromes.

2.11.1 Clinical experience in determining classification

Castori proposed that with clinical experience, and appropriate investigation, Classes 1-3 can be identified (19). Genetic testing would be required to confirm genetic syndromes in

Class 4 (19). Patients with unrecognisable syndromes and hypermobility (Class 5), usually represented rare cases, where clinical characteristics didn't fit with any particular diagnostic criteria, further investigation was required (19). This systematic approach represents the view of an experienced geneticist, and the author acknowledged the importance of clinical experience in the interpretation of signs and symptoms, as well as the challenge to diagnostic pathways, such as when to refer for genetic testing (19).

The experience of the clinician was also discussed by Remvig et al., 2011 who suggested that the ability to formulate a diagnosis, depends largely on the experience of the clinician (40). The authors reported that the usual diagnostic pathway for patients with hypermobility-related conditions was usually in the care of geneticists or rheumatologists (40). They described that Rheumatologists approach diagnosis with a focus on mobility and duration of pain, whilst Geneticists approach diagnosis with a consideration of inheritance and syndromic presentation as well as joint mobility (40).

2.11.2 Evolving diagnostic classifications

Historically, these two approaches (rheumatological and genetics) to diagnosis and evaluation appear to have driven the diagnostic classification. In the 1960's, the term Hypermobility Syndrome (HMS) was used to describe individuals presenting to rheumatology clinics, with musculoskeletal symptoms in the presence of joint hypermobility (64). Developments in diagnosis led to the Brighton criteria for 'Benign Joint Hypermobility Syndrome' (BJHS) (70) and the Villefranche criteria described for Ehlers-Danlos Syndrome including the hypermobility type (EDS-HT) (71). Following use of both criteria for the evaluation of patients with BJHS and EDS-HT, they were found to overlap, and researchers reported an inability to separate the two conditions (72). This was further demonstrated in one study, which identified 23 Italian families, which comprised of 82 individuals with JHS/EDS-HT. They found that JHS and EDS-HT were diagnosed in multiple families, with a high number of individuals meeting both sets of diagnostic criteria (73).

Several issues with the two diagnostic criteria were proposed from a clinical viewpoint including; i) lack of standardised methods to assess joint mobility considering age, sex and ethnicity, ii) lack of standard methods to assess skin features and the fact that cutaneous features had different relevance in the Brighton and Villefranche criteria, iii) lack of clear attribution of pain, iv) vague and sex biasing features such as 'eye signs', pelvic prolapse and varicose veins in the Brighton criteria, v) changing hypermobility with age, vi) evolution of pain sensations with age, vii) possible effect of chance, or time on skin features like scars, vi) impact of age and sex on associated comorbidities (72). Authors concluded by recommending that clinicians should 'shift' from a simple application of measurements to complex, multifaceted evaluations (72).

This difficulty in separating BJHS and EDS-HT led to the development of new criteria for an entity called hypermobile Ehlers-Danlos syndrome (hEDS) in 2017 (Appendix 1) (9). Individuals who didn't fit these strict criteria for hEDS were termed Hypermobility Spectrum Disorders (HSDs) (9). Additionally, four types of HSD were described: 1. Generalised (joint) HSD (G-HSD), 2. Peripheral (joint) HSD (P-HSD), 3. Localised (joint) HSD (L-HSD) and 4. Historical (joint) HSD (H-HSD) (41) (Table 2.5).

Table 2.5 Classification of Hypermobility Spectrum Disorder (HSD) (41)

Type	**Beighton Score**	**Secondary musculoskeletal involvement**	**Comments**
Generalised-HSD	Positive	One or more present	Generalised JH objectively assessed
Peripheral-HSD	Usually negative	Present	JH hands and feet
Localised-HSD	Negative	Present	JH single joints or group of joints
Historical-HSD	Negative	Present	Self-reported JH
hEDS	Positive	Possible	Strict criteria hEDS

Adapted from The EDS Society (https://www.ehlers-danlos.org). JH: Joint Hypermobility, HSD: Hypermobility Spectrum Disorder, hEDS: hypermobile Ehlers-Danlos syndrome

Even though the new criteria clearly separated those with asymptomatic hypermobility, HSD and hEDS, the authors described how clinically, this could be viewed as part of a continuum from asymptomatic hypermobility to symptomatic presentation HSD and hEDS demonstrated in Figure 2.5 (9)

Figure 2.5 The spectrum of hypermobility

HSD Hypermobility Spectrum Disorder, hEDS hypermobile Ehlers-Danlos syndrome

As described, the 2017 criteria were established by expert consensus, based on the available evidence from adult studies (74), (6). The 2017 criteria proved difficult and controversial to use in children and adolescents who were not biologically mature (72). Furthermore, classification of these terms was not based on clinical severity, or the assumption that one side of the spectrum (HSD) was more benign than the other (hEDS) (75). Determining symptom severity to potentially focus interventions on clinical need would be of greater benefit to clinicians and patients. Exploring such an approach has been proposed in adults (76).

2.12 Symptomatic hypermobility

During this time of changing diagnostic criteria and challenges and controversies surrounding its use in paediatrics, the British Society of Paediatric and Adolescent Rheumatology (BSPAR) described the term symptomatic hypermobility for children and adolescents presenting with hypermobility and musculoskeletal pain (4). Whilst acknowledging that hypermobility lay within a spectrum, authors declined to use specific diagnostic criteria to define symptomatic hypermobility. The term symptomatic

hypermobility was used in this thesis to define symptoms thought to be related to hypermobility which are not part of a genetic syndrome. In this thesis, symptomatic hypermobility defines symptomatic presentations within the spectrum of hypermobility, which includes HSD and hEDS as seen in Figure 2.5.

2.13 Prevalence of symptomatic hypermobility

The prevalence of children and adolescents with symptomatic hypermobility in Ireland is currently unknown. Changing nomenclature makes comparisons challenging. In terms of symptomatic hypermobility, a study in the United Kingdom reports that children with symptomatic hypermobility account for a large proportion of referrals to tertiary paediatric rheumatology clinics (21). A large, case-control study in Wales examined the prevalence of EDS and HSD, using a combination of the two codes EDS and JHS as reported in health and social care data sets in adolescents (<18 years) and adults (>18 years) (77). They reported a combined prevalence of 1 per 500 people, far greater than was previously stated, and also found that the rate of diagnosis was steadily increasing (77). Most of the data were collected from primary care datasets, with authors reporting that the reliability of the diagnosis could be questioned, as diagnoses were unlikely to have been given in primary care. Moore et al. (2019) reported a prevalence of generalised-HSD (previously EDS-HT/JHS) in children aged 6-12 attending physiotherapy in a community paediatric service in Ireland, to be 3.1% (49). Generalised HSD was defined as the presence of generalised hypermobility (BS ≥ 6/9) and musculoskeletal complaints of joint pain lasting >3 months or recurrent joint instability (subluxations or dislocation) (49). Previous studies using JHS/EDS-HT criteria with BS ≥4/9, reported higher prevalence (8.9%) in similar aged children (78).

2.14 Recognising symptomatic hypermobility

Symptomatic hypermobility should be promptly recognised and managed (41). BSPAR guidance focuses on the ability of a clinician to consider a broad range of possible clinical findings to recognise symptomatic hypermobility [64]. They recommend using a

biopsychosocial model to encompass the different aspects of the child or young person's presentation (4). Symptoms were presented as 'common' and 'additional but rare' (4). A wide variety of subjective and objective outcome measures were listed for 'guidance only' (4).

Paediatric Rheumatologists are highly skilled in paediatric musculoskeletal assessment and the consideration of broad differential diagnoses including hereditary disorders of connective tissues such as Marfan syndrome and other forms of EDS which may present similarly (79). They adopt a systematic approach to the musculoskeletal system based on the paediatric Gait Arms and Legs (pGALS) screening assessment, which is followed by a more detailed paediatric Regional Examination of the Musculoskeletal System (pREMS), which was developed by expert consensus (80). Both screening assessments systematically examine each anatomical region including every joint (80). Broadly the clinician is looking for signs of inflammation in terms of joint swelling, pain on palpation and any joint restrictions of movement (80). With an awareness of joint range typical in children and young people, assessment for hypermobility, occurs concurrently, during these joint assessments (80). Other systems are routinely screened to rule out different diagnoses, including a detailed cutaneous examination, as many conditions in rheumatology present with skin and tissue features (80). Recognition of symptomatic hypermobility therefore occurs following this skilled, systematic, screening process.

Outside of the paediatric rheumatology clinic, children often present to primary care GPs with musculoskeletal symptoms, where GPs report poor self-confidence in their ability to assess a child's musculoskeletal system, and inadequate training in paediatric rheumatology (81). Paediatric musculoskeletal clinical training is not always part of core training in medical schools in the UK (81). Most syllabi include only limited paediatric musculoskeletal system knowledge, and exposure to clinical experience is limited. Primary care (80) practitioners are recommended to use valid musculoskeletal screening assessments like pGALS, to screen for joint abnormalities. However, without standard references according to age, sex and ethnicity, recognising hypermobility may be a challenge. In terms of identifying other multisystem features such as skin laxity, to rule out other conditions presenting with joint hypermobility, there is also a lack of

standardised methods to assess other multisystem features such as skin involvement [44]. In the presence of symptoms from multiple systems, clinicians are required to use more extensive assessment tools to assess the extent of hypermobility-associated conditions which can present a challenge, especially outside of specialist centres.

2.15 Management of symptomatic hypermobility

Symptoms which impact on a child and young person's quality of life should be promptly recognised and managed (41). Children with musculoskeletal symptoms often present to primary care General Practitioners where the differential diagnosis is large and a thorough musculoskeletal examination is important to rule out more uncommon but severe illnesses such as Osteomyelitis, Leukaemia, and Juvenile Idiopathic Arthritis (81). The association between the presenting symptoms is not always clear, and often the child is referred onward to paediatric specialist centres (18). Depending on the initial presentation, children may present to a large number of specialist clinicians, which can also depend on the pathway for management within a particular health service. In Ireland, the current pathway for referral for children and adolescents with joint symptoms is the National Centre for Paediatric Rheumatology in Children's Health Ireland (CHI). Referrals are triaged into consultant and clinical specialist physiotherapy-led paediatric rheumatology clinics. Due to the paucity of evidence, targeted clinical pathways are lacking (20). Currently, care pathways in Ireland, are based on a number of different factors which are largely determined by access, availability of staffing across a multidisciplinary team, and clinician expertise. Waiting times are lengthy, and access to tertiary services can take a number of years (82). Once tertiary services are accessed, management commonly includes physiotherapy, occupational therapy or multidisciplinary (MDT)-led and is largely group based. Figure 2.6 demonstrates an example of a typical care pathway for children and adolescents with symptomatic hypermobility presenting to tertiary paediatric rheumatology services in Ireland.

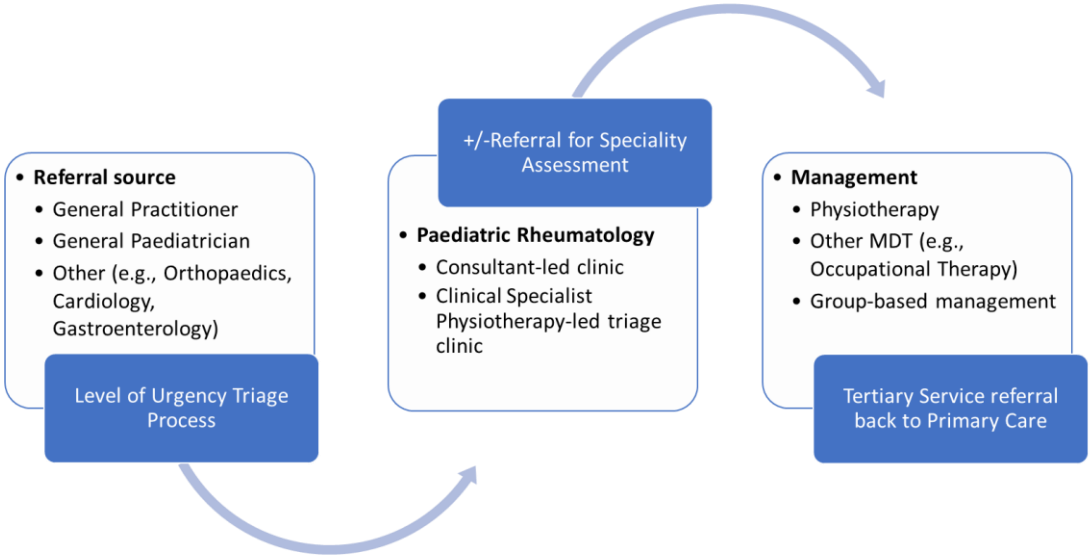


Figure 2.6 Care pathway for children and adolescents with symptomatic hypermobility presenting to tertiary paediatric rheumatology services in Ireland. MDT Multidisciplinary Team

The evidence base for physiotherapy assessment and management is limited (20). A systematic review assessed the effectiveness of conservative management for symptomatic hypermobility, including 3 paediatric studies (83). Exercise was the core component in conservative management and has been found to be superior to no-treatment controls (83). However, identifying if there are subgroups of patients that may benefit from management of different intensity is unknown (21). The targeting of treatments by using stratified care according to subgroups is reported to be central to the progress of healthcare (84). The evidence for the existence of subtypes in paediatric hypermobility, is exploratory to date (85, 86). There appears to be an opportunity to identify clinical phenotypes, to optimise health care (20).

Clinical guidelines produced by the British Society of Paediatric and Adolescent Rheumatology group in 2017 provide the general basis for therapy management and advise a multidisciplinary (MDT) approach which includes Physiotherapy (4). Guidelines recommend a biopsychosocial model of assessment (4). Management principals are based on encouraging self-management, pain management and education. More specific

guidance is tailored to the MDT, for example physiotherapy is recommended to be targeted to the individual, and comprising of a graded return to activities, exercise, postural education, strengthening, stretching, goal setting, advice, proprioceptive training and sport specific assessment (4). Further MDT guidance is provided, and resources are recommended including those for management of sleep, stress and pain (4). A randomised control trial, one of only three randomised controlled trials performed in children with symptomatic hypermobility, was conducted in 119 children aged 5-16 years, where participants were randomised to receive individual multidisciplinary intervention or standard care (21). Standard care consisted of one paediatric rheumatology appointment at clinic, where a diagnosis was made, followed by verbal information and advice regarding management and onward referral for appropriate multidisciplinary intervention if clinically appropriate [43]. The intervention consisted of 5 visits over an 8-week period, involving physiotherapy and occupational therapy, and including a home and school visit (21). Standard management was found to be sufficient to lead to sustained improvements over a 12-month period. Results found that there was no significant benefit from the multidisciplinary intervention, compared to the standard group (21). However, participants included in this study experienced less distress and disability than other cohorts (21, 87). The authors reported that due to the heterogenous study population, there may have been subgroups within the population who may have benefitted from more targeted or intensive intervention (21).

2.16 Summary

This chapter has introduced the topic of hypermobility in greater detail. Historical references to hypermobility were described. The prevalence, measurement and classification of hypermobility was introduced in a paediatric context. Genetic conditions, such as heritable disorders of connective tissues, which feature hypermobility, were illustrated. Additionally, musculoskeletal, and systemic symptoms that may be associated with hypermobility were described, along with other conditions specific to paediatrics, which may present similarly. Finally, an overview of the management of patients with symptomatic hypermobility was provided.

Chapter 3 Study I: Symptomatic hypermobility in children and young people: A systematic scoping review

This chapter presents a systematic scoping review of the published literature exploring the clinical characteristics of children, adolescents, and young adults with symptomatic hypermobility. The scoping review was the first study in this thesis (Figure 3.1). An edited version of this chapter was published in the journal *Physiotherapy Practice and Research* in March 2022 (Protocol) and January 2023 (Full review):

Ward S., MacDermott E.J., Simmonds J., Deane J., Mockler D., Dockrell S. Clinical Characteristics of symptomatic hypermobility in children and young people: A scoping review protocol. Physiotherapy Practice and Research 43 (2022) 63-69. DOI: 10.3233/PPR– 210601 (Appendix 2), and

Ward S., MacDermott E.J., Simmonds J., Deane J., Mockler D., Dockrell S. Symptomatic hypermobility in children and young people: A scoping review of clinical characteristics using a developmental framework. Physiotherapy Practice and Research 43 (2022) 223–236 DOI:10.3233/PPR-220699 IOS Press (Appendix 3).

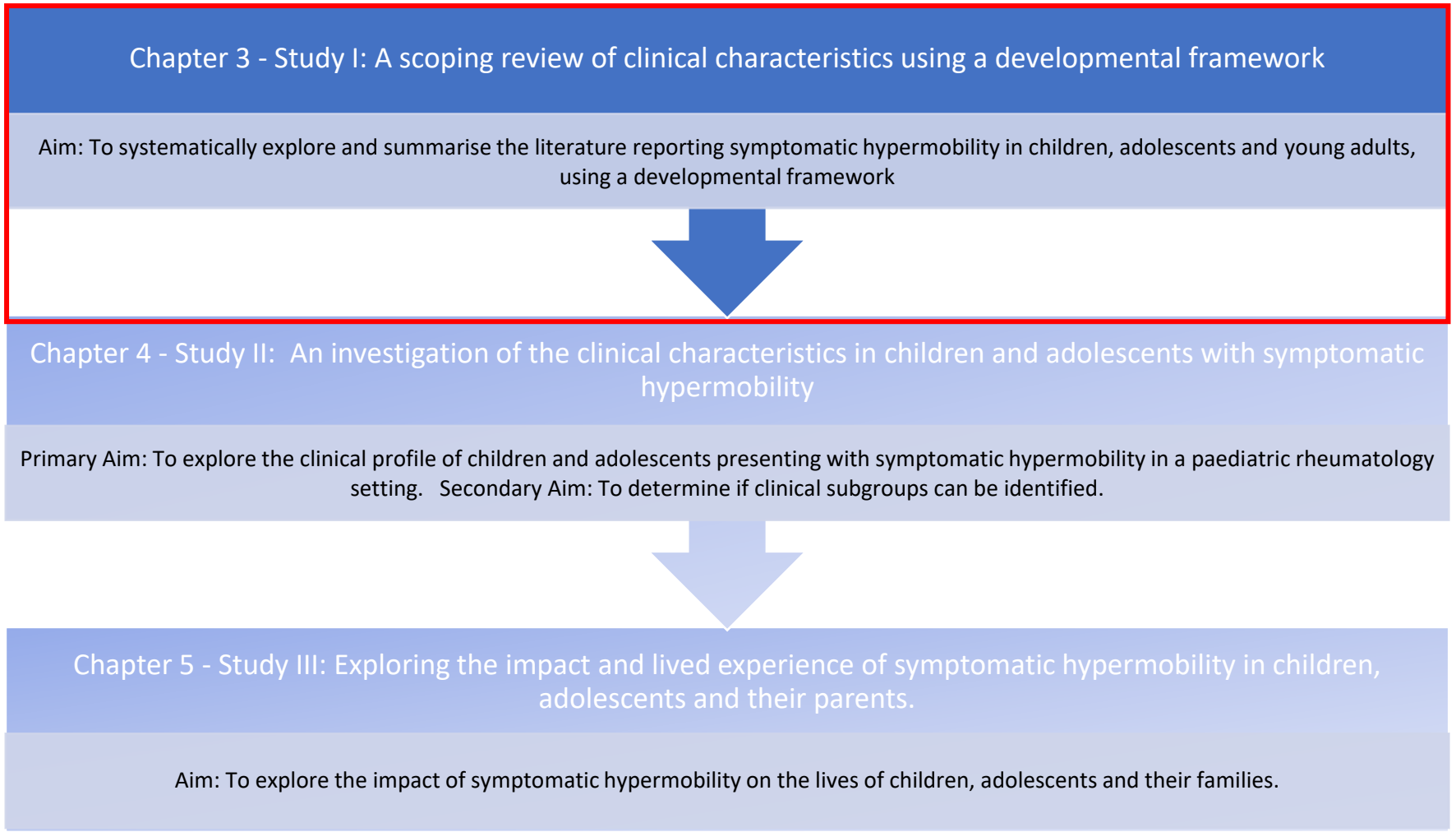


Figure 3.1 Outline of the studies in this thesis

3.1 Introduction

As discussed in Chapter 2, hypermobility is a descriptive term, not a diagnosis, as it refers to a physical trait (19). Hypermobility can be defined as the ability of a joint or a group of joints, to move beyond the typical range of movement (1). Hypermobility is sometimes described interchangeably with ligamentous laxity or joint hyperlaxity. Early literature reported that when joints are 'unduly lax' with the range in excess of the accepted norm, this can be described as having generalised hypermobility (64). However, a joint can be hypermobile without necessarily being 'lax' and the two terms are not synonymous (12).

3.2 Prevalence of hypermobility

Hypermobility is more common in children (7) and females (47). A higher prevalence has also been reported in populations of African and Asian ethnicities, although not consistently (7, 47). Increased body mass index was positively associated with generalised joint hypermobility in girls in a large UK population study of 6,022 children (mean age 13.8 years) (50). A recent systematic review reported marked differences in prevalence rates, from 3.3% in 12-13- year-old boys from Denmark to 65% in children between 3 and 13 years old in Hong Kong (48). This marked variation reflects the different populations being studied, and the varying definitions of hypermobility, and reported methods, which lack consistency (48).

3.3 Hypermobility assessment methods

Many assessment methods have been described to assess hypermobility (53). Four clinical tests (Beighton score, Carter and Wilkinson, Hospital del Mar and Rotes-Querol) and two questionnaire assessment methods (5-point questionnaires and Beighton score self-reported) were identified in a systematic review which reported the properties of these clinical assessment methods (53). Two other assessment methods (Lower Limb Assessment Scale (62) and Upper Limb Hypermobility Assessment Tool (88)) use more advanced methods and also test for multidirectional joint laxity. These assessment methods are described in detail in Chapter 2.

3.4 Recognising symptomatic hypermobility

Hypermobility can be associated with a wide variation of symptoms, or it can be part of a genetic condition (11). Genetic disorders are considered rare and can be attributed to a specific gene (11). Hereditary connective tissue disorders such as Ehlers-Danlos syndrome (EDS), Marfan syndrome and skeletal dysplasias are some of the genetic conditions associated with hypermobility and were not the subject of this review (11).

Recognising symptomatic hypermobility in children and adolescents requires a clinical assessment, and exclusion of other reasons for symptoms, as there is no specific diagnostic test (19). Children and adolescents with symptomatic hypermobility present to geneticists, rheumatologists, general paediatricians, or other specialists depending on their presenting symptoms (40). Rheumatologists are skilled at musculoskeletal assessment and the consideration of a broad differential diagnosis (18). They often focus on joint mobility and pain, which is often a presenting feature (40). Geneticists may consider ruling out other genetic causes, considering other forms of EDS for example (40). Assessments must be interpreted in the context of normal variants and symptoms, such as pain (8), that may be common in the general paediatric population (18). The wide variation in the presenting clinical characteristics in children with symptomatic joint hypermobility presents a challenge to this clinical diagnosis. As individuals are often not diagnosed until late adolescence or early adulthood, interpreting presenting symptoms in children and adolescents is challenging (69).

3.5 Terminology

The terminology used to define hypermobility with symptoms has changed a lot over the years (Figure3.2). The association of hypermobility with musculoskeletal symptoms was first termed Hypermobility Syndrome (HMS) by rheumatologist Kirk and colleagues in 1967, and this was later referred to as BJHS (64). One variant of EDS, hypermobile Ehlers-Danlos syndrome (hEDS) previously termed Ehlers-Danlos type 3 (EDS type III) and Ehlers-Danlos syndrome hypermobility type (EDS-HT), is not confirmed by molecular testing and is diagnosed using clinical criteria (11). Different diagnostic criteria: Brighton criteria for BJHS (70) and the Villefranche criteria for EDS-HT (89) were described to help identify

symptomatic hypermobility. In 2017, a new nosology was developed by international consensus (41). The terms 'hypermobile Ehlers-Danlos syndrome (hEDS)' and 'Hypermobility spectrum disorder (HSD)' were proposed with strict criteria defining hEDS, whilst HSD was more loosely categorised into phenotypically different forms (9, 12, 19).

The term symptomatic hypermobility, as described by the British Society of Paediatric and Adolescent Rheumatology (BSPAR) was adopted for children and adolescents presenting with symptomatic hypermobility and musculoskeletal (4). This term was used in this scoping review to include HSD and hEDS and other equivalent diagnoses (Figure 3.2).

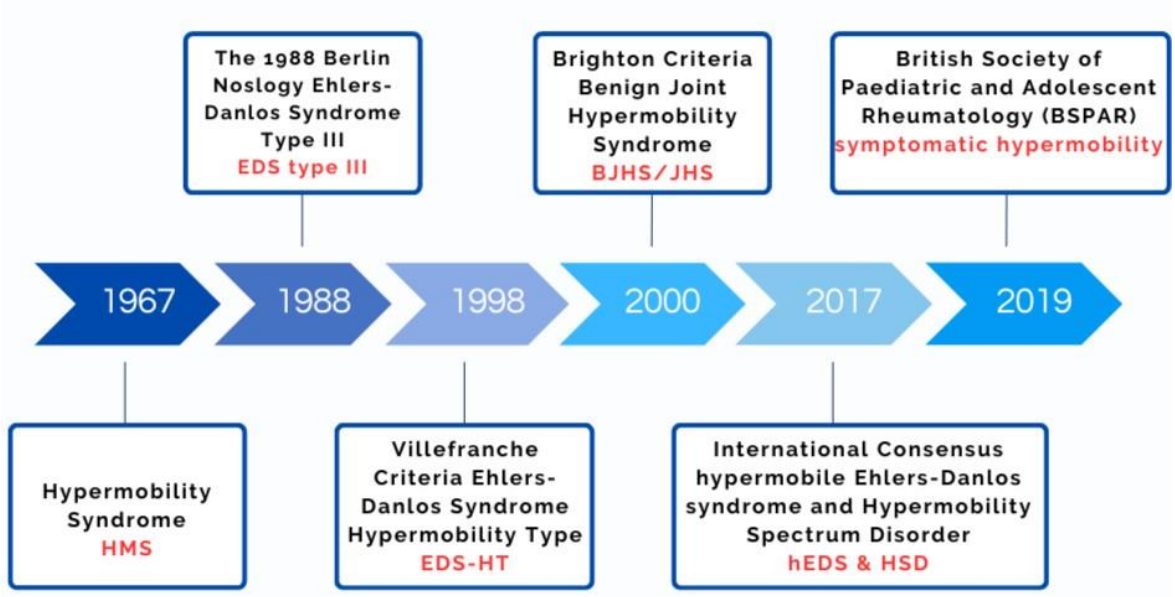


Figure 3.2 Historical trends in the terminology of symptomatic hypermobility

3.6 Natural history of symptomatic hypermobility

The natural history of symptomatic hypermobility has been proposed (90). Castori et al., 2011, described a three-phase model, from marked ligamentous laxity in the first 'hypermobility phase', followed by a 'pain phase' starting in the second decade of life (90). The third 'stiffness phase' was marked by dramatic reduction in hypermobility, multisystemic presentations such as unrefreshing sleep and chronic fatigue (90). Adult participants were recruited from specialist hypermobility clinics, and asked to recall 20 key symptoms, and indicate the approximate age at onset of the symptoms. This

methodology is subject to recall bias, and used subjective questionnaires designed by the authors (91). However, this early work hoped to nurture future research examining the phenotypic variability of symptomatic hypermobility (91). In the following decade, changes to nomenclature, inconsistencies in cut-off points, and difficulties applying diagnostic criteria to paediatric cohorts may have hampered further exploration of this changing phenotype. Literature uses varied terminology, spans medical domains and settings, and many studies include both adult and paediatric populations (11), making the interpretation of the paediatric data difficult.

3.7 Children and young people

Children and young people are defined in this review as those from birth to 24 years of age (38). The World Health Organisation (WHO) defines three developmental stages for children and young people as follows: childhood 0-9 years, adolescence 10-19 years and young adulthood 20-24. Young or emerging adulthood is now recognised to be a time of neurological maturation and psychosocial development alongside increasing disease burden and health risks such as sexual and mental health and was included in this review (34, 92).

3.8 Scoping Review or Systematic Review?

Knowledge synthesis is a phenomenon that has been observed since the 12th century in philosophical texts, and in scientific literature since the 17th century (93). Systematic reviews have been well established in medical literature, notably involving the Cochrane Collaboration (93). However, traditional systematic review methods are not always appropriate, when addressing topics of complexity, or broad research questions (93). Hence, scoping reviews can be suitable when aiming to summarise a heterogenous body of knowledge, across methods, or disciplines, and are often used to determine the need to undertake a systematic review (94). An early methodological framework was proposed by Arksey and O'Malley, (95) and later updated (96). Following this original framework, further guidance was then published by the Joanna Briggs institute (JBI) in 2015, which

was based on Arksey and O'Malley's framework and emphasised the importance of methodological rigour (97). Arksey and O'Malley's original framework is described in 5 stages, which was adopted for this scoping review (Figure 3.3). Whilst these phases appear linear, the process is encouraged to be iterative, including consultation and engagement in an iterative way, to adapt to findings, and repeating steps if necessary (95). It is well documented in scoping review (ScR) frameworks, that the included sources of evidence are not typically appraised (94). Scoping reviews do not formally evaluate the quality of evidence, such as undertaking a risk of bias assessment (98), as they are exploratory and descriptive in nature.

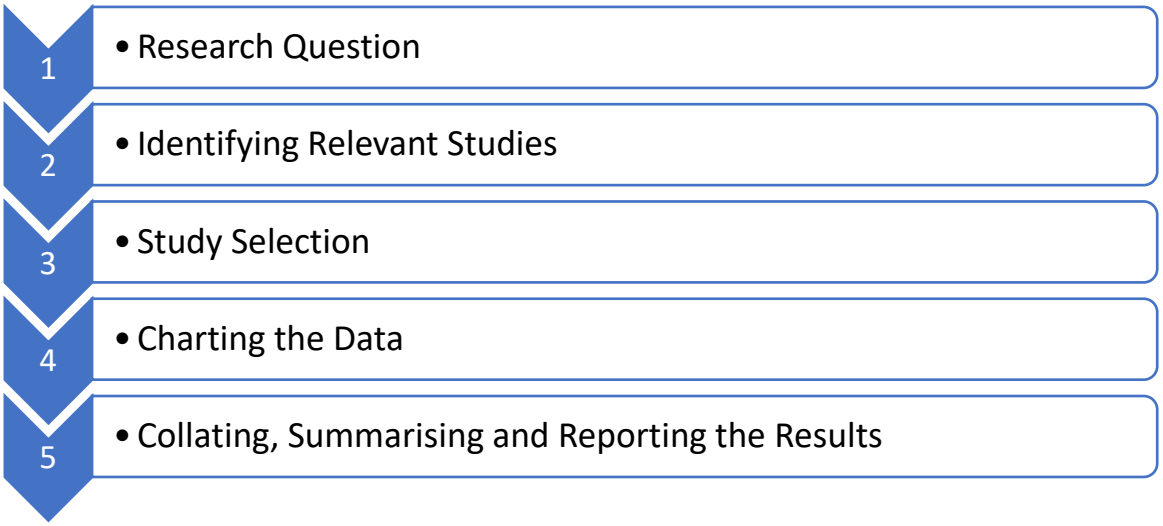


Figure 3.3 Arksey and O'Malley 5 stage Framework (95)

3.9 Framework stage 1: Research question

This review was guided by the research question "What are the presenting clinical characteristics of children, adolescents and young adults with symptomatic hypermobility (including HSD and hEDS and other equivalent diagnoses)?"

3.9.1 Aims and objectives

The purpose of this scoping review was to systematically explore and summarise the literature reporting symptomatic hypermobility in children and young people, which is the first aim of this thesis.

The objectives were to report:

i) study designs and settings
ii) population characteristics
iii) diagnostic criteria and measurement approaches
iv) clinical characteristics identified in the context of developmental stages (childhood (0-9 years), adolescence (10-19 years), and young adulthood (20-24 years)).

3.9.2 Materials and methods

A scoping review (ScR) approach was identified as the methodology suitable to the research question, aims and objectives of this study (95). The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) extension for Scoping Reviews (PRISMA-ScR) was used when carrying out this scoping review (Appendix 4) (24). This reporting guide was designed by an expert panel and consisted of a checklist and explanation to encourage good reporting of a minimum number of items (24). This checklist supported transparency and was included in the manuscript upon protocol registration and subsequent publication (99).

3.9.3 Eligibility criteria

The Population, Concept and Context (PCC) framework was used to determine study eligibility, following the development of the research question (Table 3.1) (97).

3.9.4 Inclusion criteria

The population was children and young people from birth to 24 years. Including emerging adulthood up to 24 years reflected the overlapping terms of adolescence and youth, captured by the term 'young people' (38). Inclusion of both children and young adult participants ensured that search terms were not restrictive to age limits initially, to allow for inclusion of studies which included a mixed age-group cohort. Children and young people with a clinical diagnosis of symptomatic hypermobility, HSD, hEDS or equivalent

diagnoses (EDS-HT, EDS type III, BJHS and JHS) using internationally recognised criteria were included. Studies of children and young people with a confirmed diagnosis following a clinical assessment which took place in a clinical setting were included in the review. Studies conducted by clinical researchers using clinical assessments in school or university settings were also included. Randomised and non-randomised controlled trials, intervention, and observational studies including case reports were included. Review articles were included if they fulfilled the inclusion criteria and presented data not seen in original articles. Case reports were included, although with an awareness that they can often represent more severe presentations. Including a broad range of studies is in keeping with the ScR methodology and the aims to explore the full spectrum of the literature.

3.9.5 Exclusion criteria

Studies of other Hereditary Diseases of Connective Tissue (HDCT) including other types of Ehlers-Danlos syndrome (EDS) were excluded if results from the HSD/hEDS group could not be separated. There are a number of genetic syndromes, most of which present with recognisable features which include JH. These syndromes include Marfan syndrome, Stickler syndrome, Loeys-Dietz syndrome, and others (19). Studies that included participants with these syndromes were excluded from this scoping review. As JH is a common trait in children and young people, studies describing asymptomatic JH were also excluded. Review articles were excluded if on searching the primary source, the original data no longer fulfilled the inclusion criteria. Editorials, opinion papers, abstracts and posters were not included. Studies written in languages other than English were excluded. Studies where there was an inability to obtain the full text were also excluded.

Table 3.1 Population, Concept and Context (97)

TABLE 1	Inclusion	Exclusion
Population	Children and young people aged 0-24 years with diagnosis of Symptomatic Hypermobility, HSD, hEDS or equivalent diagnosis EDS-HT, EDS type III, JHS or BJHS' using internationally recognised criteria.	Studies of other forms of Ehlers-Danlos syndrome, and other genetic syndromes which present with recognisable features, including joint hypermobility such as Marfan syndrome, Stickler syndrome, Loeys-Dietz syndrome, and others. Studies describing asymptomatic joint hypermobility
Concept	Clinical diagnosis by a health care practitioner	Diagnosis by self-report (questionnaire).
Context	Studies from any country, published in peer review journals, including randomised and non-randomised controlled trials, intervention, and observational studies including case reports.	Editorials, opinion papers, abstracts, and posters. Studies with lab or genetic findings only.
	Reviews if they fulfil the inclusion criteria and capture data not seen in original articles.	Studies without any reported clinical characteristics.
Language	English.	Not in English language.

3.9.6 Protocol and registration

The ScR protocol (99) was developed before conducting the full scoping review to ensure transparency and was registered with the Open Science Framework (OSF) on 20th September 2021 (https://osf.io/m2h6q). The OSF is an open platform, which encourages the sharing and collaboration of research processes (100). In this case, it allowed for open access to the ScR protocol and allowed authors to track the impact (100). The protocol

described each step of the review process, provided details regarding how decisions were made, aligning with the frameworks discussed earlier, following quality reporting criteria (94, 95, 101).

3.10 Framework stage 2: Identifying relevant studies

The search strategy was formulated by the key concepts contained within the research question; i) symptomatic hypermobility, ii) clinical characteristics, and iii) children and young people. Meetings were conducted with an expert subject librarian to discuss the search terms and strategy. Each concept was discussed to consider synonyms, database-controlled vocabulary to avail of the truncation system, and consideration of phrase searching. Further discussions assisted the development of search terms, to consider Boolean operators which allowed the building of supersets for consideration. Terms synonymous to hypermobility such as double jointed, joint laxity, hypermobility-related-disorders, and flexibility were considered. An initial search of the term hypermobility without links revealed >7,000 studies. As an iterative process, this search strategy was refined following discussion with the wider research team, experienced clinicians and an experienced subject librarian, as advised by Levac et al., 2010 who stress the importance of a team approach (102). It was decided not to include hypermobility or joint laxity as a specific term (except as a controlled vocab in the database EMBASE). No limits on date or language were placed on the initial database searches, to ensure that as broad a search as possible was conducted, as per the aim of the scoping review. A series of systematic searches were carried out with refined search criteria and the final search strategy was decided (Table 1). The final search was carried out from inception to June 2021, so that historical articles, including seminal papers, would be included. The strategy used Boolean Operators across four main databases: Cumulative Index of Nursing and Allied Health Literature, PubMed, Embase and Web of Science (Table 3.2). These databases were selected to be comprehensive and to cover a broad range of medical disciplines. All information sources were included in the search.

An extended search was conducted which included manually searching grey literature (www.opengrey.eu) and targeted websites (www.ehlers-danlos.com;

www.hedstogether.com; www.hypermobility.org) using refined search terms (Table 3.2). The Google search engine (www.google.com) was used to conduct a search without date restriction. The first 20 hits (deemed most relevant by the Google search engine) were screened. Each review article was hand searched to identify articles not yet captured.

The final search was uploaded into EndNote and duplicates were removed. The citations were imported from EndNote into a web-based bibliography manager, Covidence™ software, 2016 (www.covidence.org). Covidence™ is software designed for the literature review process, to enable a systematic, collaborative approach. Specific inclusion and exclusion criteria were entered onto Covidence™ and the review process was conducted as described in the á priori, published scoping review protocol (99) (Appendix 2).

Table 3.2 Search Strategy

SEARCH DATABASE
EMBASE Search Terms
'Ehlers-Danlos syndrome hypermobility type'/exp OR ('Ehlers-Danlos syndrome'/exp AND ('joint instability'/exp OR 'hypermobility'/exp OR 'joint laxity'/exp)) ((ehlers–Danlos OR 'spectrum disorder*' OR symptomatic OR syndrome) NEAR/3 hypermobil*):ti,ab ('Hypermobile EDS' OR 'hEDS' OR 'Hypermobility spectrum disorder' OR 'Ehlers-Danlos syndrome hypermobility type' OR 'EDS-HT' OR 'Joint hypermobility syndrome' OR 'JHS' OR 'Ehlers-Danlos Type III'):ti,ab ('conference abstract' OR 'conference review' OR letter):it #1 OR #2 OR #3 #5 NOT #4
Medline Search Terms
Ehlers-Danlos Syndrome/ AND Joint Instability/ ((Ehlers Danlos OR spectrum disorder* OR symptomatic OR syndrome) adj3 hypermobil*). ti,ab. (Hypermobile EDS OR hEDS OR Hypermobility spectrum disorder OR Ehlers-Danlos syndrome hypermobility type OR EDS-HT OR Joint hypermobility syndrome OR JHS OR Ehlers-Danlos Type III).ti,ab. or/1-3
CINAHL Search Terms
(MH "Ehlers-Danlos Syndrome") AND (MH "Joint Instability+") TI ((Ehlers–Danlos OR "spectrum disorder*" OR symptomatic OR syndrome) N2 hypermobil*) OR AB ((Ehlers–Danlos OR "spectrum disorder*" OR symptomatic OR syndrome) N2 hypermobil*) TI ("Hypermobile EDS" OR "hEDS" OR "Hypermobility spectrum disorder" OR "Ehlers-Danlos syndrome hypermobility type" OR "EDS-HT" OR "Joint hypermobility syndrome" OR "Ehlers-Danlos Type III") OR AB ("Hypermobile EDS" OR "hEDS" OR "Hypermobility spectrum disorder" OR "Ehlers-Danlos syndrome hypermobility type" OR "EDS-HT" OR "Joint hypermobility syndrome" OR "Ehlers-Danlos Type III") S1 OR S2 OR S3
Web of Science Search Terms
TI =(((("Ehlers Danlos" OR "spectrum disorder*" OR symptomatic OR syndrome) NEAR/2 hypermobil*) OR ("Hypermobile EDS" OR "hEDS" OR "Hypermobility spectrum disorder" OR "Ehlers-Danlos syndrome hypermobility type" OR "EDS-HT" OR "Joint hypermobility syndrome" OR "Ehlers-Danlos Type III")) OR AB =(((("Ehlers Danlos" OR "spectrum disorder*" OR symptomatic OR syndrome) NEAR/2 hypermobil*) OR ("Hypermobile EDS" OR "hEDS" OR "Hypermobility spectrum disorder" OR "Ehlers-Danlos syndrome hypermobility type" OR "EDS-HT" OR "Joint hypermobility syndrome" OR "Ehlers-Danlos Type III"))
Refined Search Terms
Symptomatic OR Syndrome Hypermobility, Hypermobile EDS, Hypermobility spectrum disorder, Ehlers-Danlos syndrome hypermobility type, Joint hypermobility syndrome, Ehlers-Danlos Type III

3.11 Framework stage 3: Study selection

A two-stage process was followed, whereby title and abstract screening and full text reviewing were conducted in Covidence™ by two independent reviewers. Reviewers met at regular intervals to discuss any challenges or uncertainties relating to the study selection. The first phase was title and abstract screening. For each study, inclusion and exclusion criteria were reviewed. Studies satisfying criteria were included to full text review. Studies which failed to satisfy criteria were excluded with justification recorded using Covidence™ software. This process was anonymous to each reviewer to reduce bias. All citations deemed relevant for full text review were obtained via academic institution holdings, by long term loan, or by contacting the principal author if assistance was required. Principal authors were also contacted if there was missing data in full text or where further clarity was required e.g., study participant characteristics. Full text review subsequently followed a similar process: full texts were uploaded for each study, reviewed independently by two reviewers, considered for inclusion based on strict criteria, and notes made to justify reasons for exclusion.

3.11.1 Inter-rater reliability study

Two independent reviewers (Principal Investigator and PhD Supervisor) conducted the two-stage review process. Inter-rater reliability was tested at both title and abstract and full text stages to substantial agreement (Cohen's Kappa=0.7) (103). Using recorded notes, any conflicts were discussed face-to-face, or online, following each stage. The nature of the discussions were based on the individual interpretation of the inclusion and exclusion criteria rather than the need to modify the criteria (104). Clarity was also needed regarding some of the clinical points related to the diagnostic criteria. Any further conflicts were resolved with a third member of the wider research team (Co-supervisor) who reviewed three conflicts which had not been resolved between the first two reviewers.

3.12 Framework stage 4: Charting the data

In a systematic review, this process is called 'data extraction' and may involve statistical technique, but the approach used in a ScR is referred to as a data charting process, taking a broad view. A risk of bias assessment of studies was not performed, which is in keeping with ScR methodologies (105). However, study designs were plotted in terms of levels of evidence. A data charting template was developed to determine which variables would best answer the research question (102).

3.12.1 Pilot study

Two independent reviewers conducted a pilot data charting with 20 randomly selected studies. Meetings were held during this pilot process, to determine if the data charting was consistent with the research question. Following this pilot study, minor modifications were made, specifically, data charting templates were created which were specific to study design. Separate final data charting templates were created for empirical studies (author, year, country, participants, methods, relevant findings), narrative reviews (author, year, diagnostic criteria, relevant findings) and systematic reviews (author, year, number of studies, relevant findings). When consensus was achieved, one reviewer completed the data charting process.

3.12.2 Data charting

The data were coded and grouped, and a narrative account of the data was presented. The data were categorised into three main areas: (i) mapping of clinical characteristics according to clinical domains in an age, sex, and developmental context; (ii) detailed descriptions of specific eligibility , diagnostic criteria and outcome measures used including any evidence of standardisation such as standardised testing positions, or use of goniometry, and (iii) numerical listing of country in which the studies were conducted, publication date, journal type, clinical setting and study design. Where studies covered more than one clinical domain, they were placed and described within the domain that predominantly suited the main aim of the original study.

3.12.3 Data management and analysis

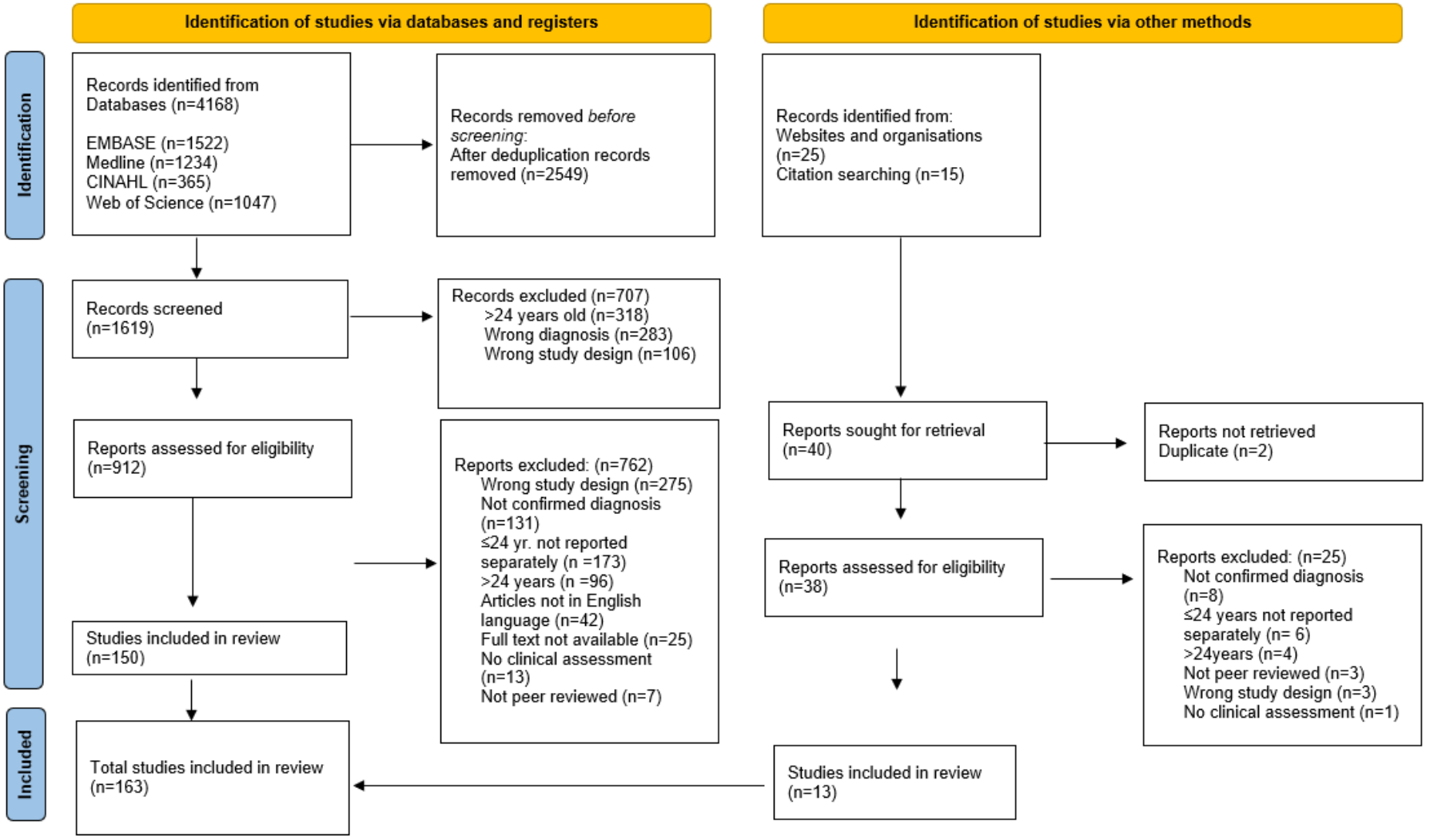
The data were compiled using the created templates which were embedded within Covidence™, and then imported in Microsoft Excel (Microsoft 360). Data were cleaned and screened within Excel, and descriptive statistics were calculated to summarise the data and frequencies and percentages were used to present nominal data (104).

3.13 Framework stage 5: Collating, summarising, and reporting the results

The scoping review was conducted over 12 months from January 2021-2022. The protocol was written and reviewed over the first 6 months before data charting was conducted. The protocol was registered with OSF, and furthermore was published in early 2022 (99). The original search generated 4168 papers. Following deduplication, 1619 titles and abstracts were screened, and 912 full text articles were reviewed of which 150 were included in the analysis. The extended search was carried out in June 2021, and this yielded a further 13 papers. Despite numerous attempts to procure all studies using various institute sources and contacting primary authors, n=25 studies were unable to be found and were not included in the review. Due to the large amount of literature spanning five decades, reference is often made to the temporal nature of the included data, due to the significant changes which occurred over time.

Many studies were excluded upon screening at title and abstract level if they were the wrong study design, or wrong diagnosis such as a different subtype of EDS. Studies were excluded at full text stage if it was not possible to extract data for participants ≤24 years (n=173), or if the population was > 24years. The study selection process including the full list of reasons for exclusion at full text stage, is presented as a PRISMA-ScR flow diagram (Figure 3.4). This process required scrutiny and was a time-consuming process since there was great diversity amongst the included studies. In total, 163 studies were included in the scoping review. Complete summaries of all included studies, categorized by study design, are presented in Appendix 5.

Figure 3.4 PRISMA-ScR flow diagram of study selection process (24)



3.13.1 Context

Empirical studies (n=108) were conducted in 26 different countries, but nearly 50% were carried out in the US (29%) or UK (20%), followed by Italy (9%). The Netherlands and Sweden had 4 publications each and other European countries included representations from 8 other countries including Ireland. There were 11 studies from Australia and 8 from Asia. Studies reporting clinical characteristics for the cardiovascular domain, were predominantly (53%) published in the US (106-114). There was one international collaboration (115) including children from 3 different cohorts in The Netherlands, Belgium and Australia, on the basis of convenience sampling (115). The majority of studies show a trend towards Caucasian populations.

3.13.2 Study design and publication dates

Of the 163 studies, 108 were empirical research, consisting of observational studies (n=45,28%), case reports/series (n=39,24%) and retrospective chart reviews (n=17,10%). Randomised controlled trials and qualitative studies accounted for n=3, n=4 (4%) respectively (Figure 3.5). Only n=2, 1% of papers were longitudinal in design describing the natural history of complaints and disability in 101 children with symptomatic hypermobility (116) and children aged 8-13 with symptomatic hypermobility (n=14) within a larger study investigating musculoskeletal pain across puberty (117). Of the non-empirical studies, 30% (n=49) were literature and narrative reviews and 4% were systematic reviews (n=6) (Figure 3.5). Of the six systematic reviews, only one was specific to children alone, reviewing the evidence for interventions for lower limb problems in children with symptomatic hypermobility, but this review included only two papers, citing the lack of high-quality intervention studies in the area (118).

Publication dates spanned from 1967 to 2021. The majority of papers (n=120, 74%) dated from 2010 (Figure 3.5). All of the systematic reviews, randomised controlled trials and longitudinal cohort studies were conducted in the period from 2010-2019, peaking around 2017. The period from 2020-2021, although just a short period, is predominantly narrative and retrospective reviews, similar to earlier publication periods.

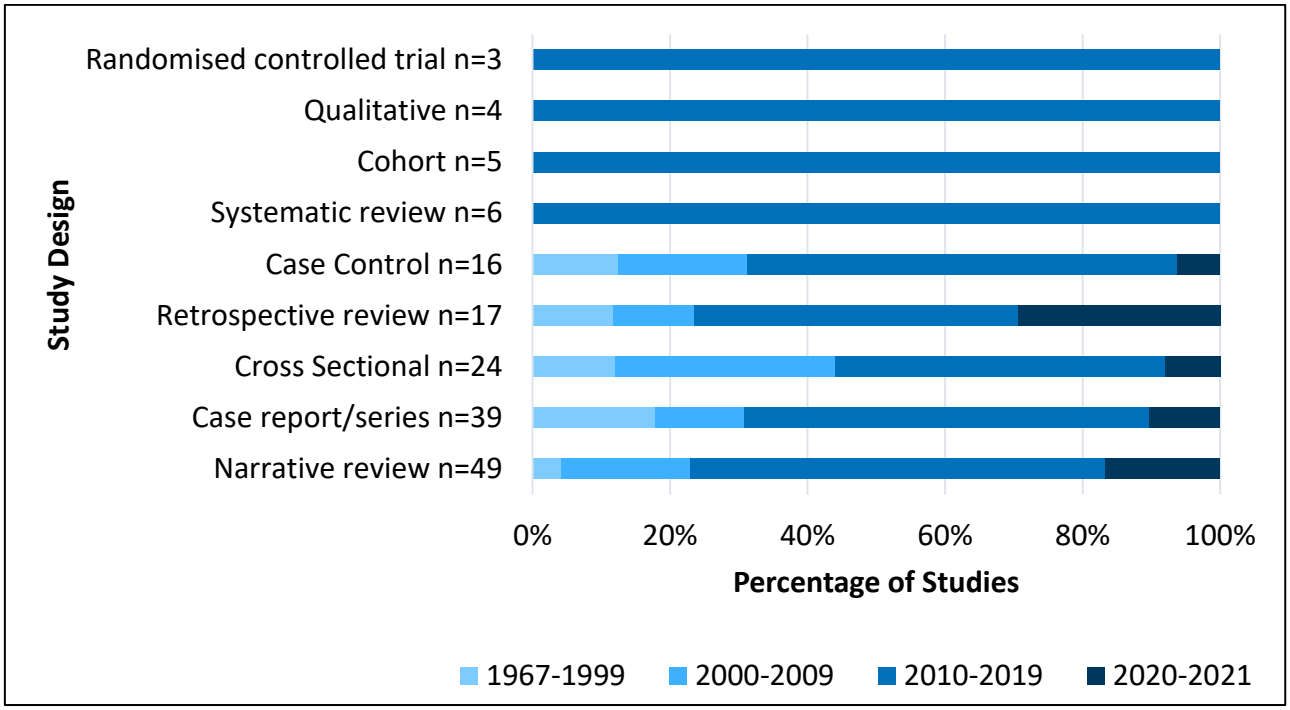


Figure 3.5 Study Design and Publication Dates

3.13.3 Study design and quality

Using a simple hierarchical approach (119), study designs were plotted predominantly at a lower level of evidence with narrative/literature reviews and case series/reports accounting for 88 (54%) of the included studies (Figure 3.6).

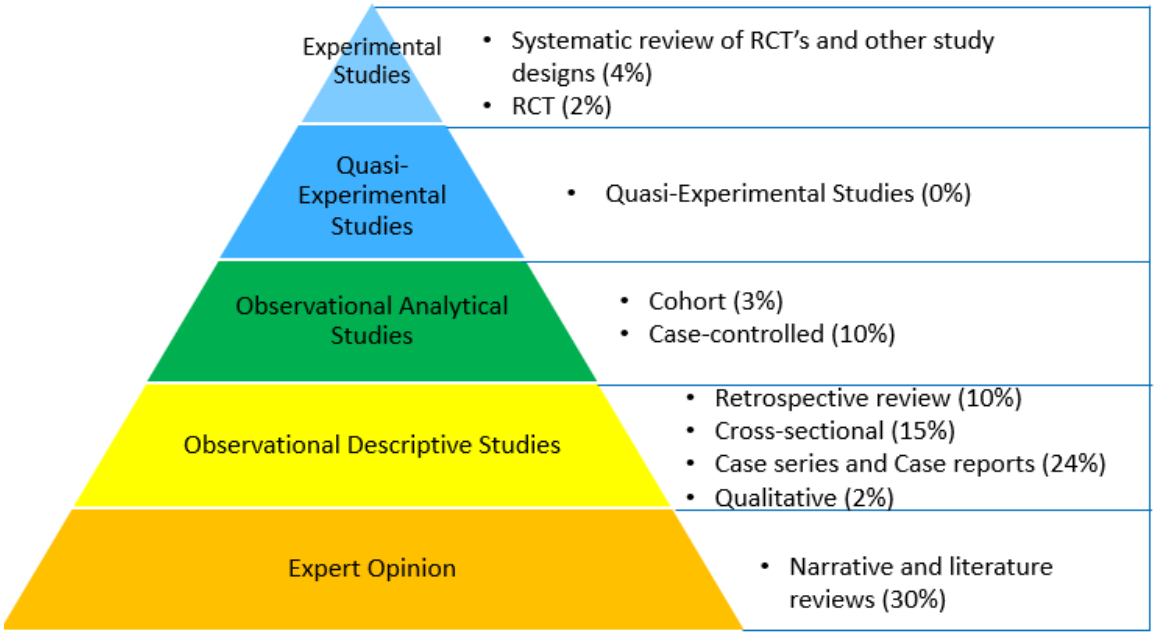


Figure 3.6 Study design by hierarchy (119)

3.13.4 Journal type

The types of journals publishing studies included in this review spanned over 25 different domains from medical, surgical, and psychosocial spheres including both general and specialised topics (Figure 3.7). Within the musculoskeletal domain, orthopaedic, physical therapy and rheumatology journals accounted for nearly 40% (n=65) of studies.

3.13.4.1 Type of journal and year

Rheumatology-specific journals (n=31, 19%) including paediatric rheumatology journals (n=7) were the most likely journal type to be included in the scoping review and they dated from the earliest publications (64) to the later publications (12) included in the review. Genetic journals (n=17) included an early publication (120) but over 70% (n=13) were conducted since 2015. Journal types under the heading 'Other medical' in Figure 3.7, included the Journal of Sleep Medicine (121, 122), International Journal of Eating Disorders (123) and Autonomic Neuroscience (108), representing the extension of literature into other clinical domains in the past two decades.

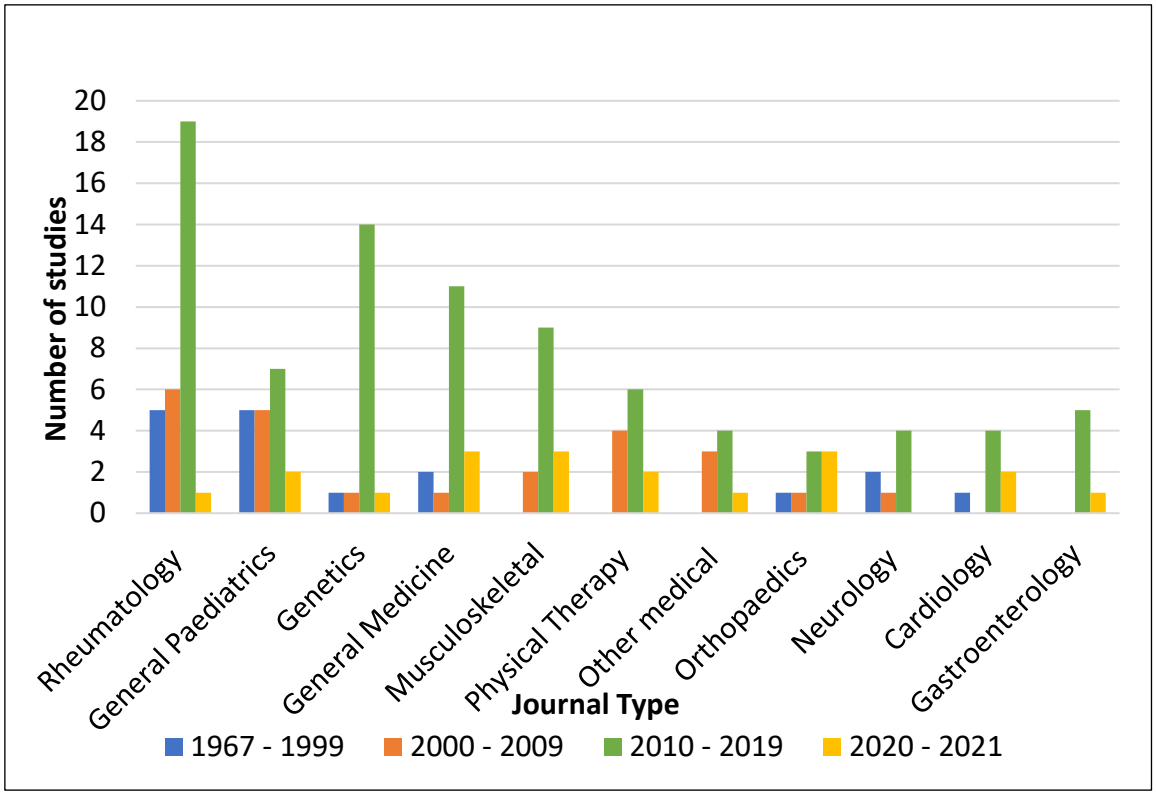


Figure 3.7 Type of Journal and Year of Publication

3.13.5 Study settings

Of the empirical studies, 94% (n=101) were conducted in clinical sites, mostly in specialist, tertiary clinical settings, and 4% (n=6) were conducted in school settings. Rheumatology was the most common clinical setting, followed by physiotherapy, genetics and paediatrics.

3.13.6 Diagnostic criteria

The diagnostic criteria used to define symptomatic hypermobility varied, but often corresponded to the diagnostic criteria at the time of publication, or the setting, such as Hypermobility Syndrome (HMS), which was used in rheumatology, rather than genetic settings (64) (Table 3.3). Over time, the clinical boundaries surrounding the diagnostic criteria for JHS and EDS-HT were argued to overlap, and both rheumatologists and geneticists agreed that they should be considered the same condition (10).

Upon further scrutiny, it was found that studies often differed in their interpretation of specific diagnostic criteria, for example, 'arthralgia for three preceding months or more' (124), 'presence of JH and musculoskeletal pain' (125), 'lower limb pain and/or fatigue in the previous 4 weeks' (126), 'presence of multiple joint pain' (127), and 'musculoskeletal symptoms (arthralgia in 2 joints for 12 weeks), exercise induced pain and exercise intolerance' (128). This may reflect the lack of detail contained in diagnostic criteria or signify the challenges using the criteria in the paediatric setting (70).

Table 3.3 Diagnostic criteria and year of publication

Diagnostic Criteria	**Count of studies n (%)**	**Years of Publication**
Joint hypermobility with symptoms (including hypermobility syndrome HMS)	29 (18)	1967-2019
EDS III	8 (5)	1985-2008
Brighton Criteria (BJHS/JHS)	44 (27)	1998-2021
Brighton (BJHS/JHS) and Villefranche (EDS-HT)	31 (19)	2005-2020
Villefranche (EDS-HT)	22 (13)	2011-2020
2017 criteria hEDS and HSD	29 (18)	2017-2021
Total included studies	n=163	1967-2021

HMS Hypermobility Syndrome; EDS III Ehlers-Danlos syndrome Type III, BJHS/JHS Benign Joint Hypermobility Syndrome/Joint Hypermobility Syndrome; EDS-HT Ehlers-Danlos syndrome Hypermobility Type; hEDS hypermobile Ehlers-Danlos syndrome, HSD Hypermobility Spectrum Disorder

3.13.7 Measurement approaches

More than 75 different measurement approaches were reported across multiple clinical domains (Table 3.4).

3.13.7.1 Measurement approaches in the musculoskeletal domain

Measurements in the musculoskeletal clinical domain were most common. Measurements of pain were reported in 14% (n=23), measurements of function were reported in 9% (n=14) and measurements of motor control, proprioception and balance

were reported in 7% (n=11). Hypermobility screening assessments were reported in 62% (n=101) of studies. Of these, the Beighton score was most commonly used (93%, n=94). There were seven other methods of assessing hypermobility. These were Beighton and Horan (129, 130), Lower Limb Assessment Scale (LLAS) (85, 131), Bulbena/Del Mar scale (21, 66, 132, 133), Carter and Wilkinson (64), Hakim and Grahame questionnaire (134), Contompasis (135, 136) and Shiari-Javadi criteria (137). Papers sometimes reported using two measures of assessing joint hypermobility (131, 134).

3.13.7.2 Measurement approaches in other clinical domains

Cardiovascular assessments were reported in 12% (n=19) papers (106-108, 111-114, 120, 136, 138-147). Other clinical domains included cutaneous, genetic, urogenital, gynaecological, and gastrointestinal. Assessments relating to quality of life were reported in 8% (n=13) of studies (21, 85, 87, 116, 121, 124, 131, 148-153) and fatigue was assessed in 6% (n=9) of studies (87, 114, 116, 149, 151, 153-156).

Table 3.4 Measurement approaches across clinical domains

CLINICAL DOMAIN	MEASUREMENT APPROACH
Musculoskeletal	
Joint Hypermobility screening	Beighton score; Beighton and Horan; Bulbena score; Lower Limb Assessment Scale; Carter and Wilkinson; Hakim and Grahame Questionnaire; Contompasis; Shiari-Javadi criteria
Pain	Pressure pain thresholds; Chronic MSP standardised questionnaire; Pain diary; Pain VAS/NRS; Peds QL Pain; BAPQ; Widespread Pain Index; Coloured Analogue Scale;PFSD
Strength/Endurance	Leg lift timed (Part of CMAS); Dynamometer
Posture/Muscle Length	FPI; Posture assessment; Hamstring length
Function	FDI; Gait assessment; Number of flights of stairs in 2 mins; 6MWT Gait analysis GAITRite; 6-minute shuttle test
Motor control, proprioception and balance	Developmental Co-ordination Disorder Questionnaire; YBT; BOT-2 balance subset; M-ABC; KTK; Multiple single leg hop test; Fundamental movement skills assessment; Joint proprioception assessment; Survey motor skills and co-ordination; Static/dynamic balance; Postural sway
Upper Limb	PODCI; DASH
Bone densitometry	Quantitative Ultrasound
Cardiac	Primary focal hyperhidrosis assessment; ECG; ECHO; Tissue Doppler Image; CT scan; Autonomic testing protocol for orthostatic intolerance 10-minute standing test
Cutaneous	Skin/superficial connective tissue stretchiness; Skin extensibility/elasticity; Presence of scars/stretch marks; Skin biopsy

Genetic	Genetic study/ testing
Ophthalmic	Ophthalmic assessment
Neurological	Neurological assessment; Muscle biopsy
ENT	Assessment for dysphonia (video laryngoscopy)
Urinary	VCUG; Drinking and voiding diary
Gynaecological	Gynaecological exam/standardised questionnaire
Gastrointestinal	ROME criteria
Psychosocial	
Psychological	Psychological well-being assessment; Family functioning assessment; The PROMIS (Pediatric Anxiety Symptoms and Depressive Symptoms short form)
QOL	PedsQL Generic Core; Child health utility 9-dimensional assessment; CHQ; BIPQ
Participation and Activity	Activity Diary; FPQ; PAQ; Physical Activity Recall Questionnaire
Other Clinical Areas	
Fatigue	The PROMIS Pediatric Fatigue (Tired) short form; Peds QL Multidimensional fatigue scale questionnaire
Headaches	2013 International Classification of Headaches disorder assessment
Sleep	SRBD; ESS; Home portable sleep test
Somatic Symptoms	Symptom Severity scale

MSP Musculoskeletal Pain, VAS Pain Visual Analogue Scale, NRS Pain Numerical Rating Scale, Peds-QL Pain Paediatric Pain Questionnaire, BAPQ Bath Adolescent Pain Questionnaire, PFSD Pain-Frequency-Severity-Duration Scale; CMAS Childhood Myositis Assessment Scale, FPI Foot Posture Index, FDI The Functional Disability Inventory, 6MWT six-minute-walk-test, YBT Y-balance Test, BOT-2 Bruininks-Oseretsky test of motor proficiency**,** M-ABC Movement Assessment Battery for Children, KTK Korperkoordinationstest fur Kinder PODCI The Paediatric Outcomes Data Collection Instrument, DASH Disabilitites of the Arm, Hand and Shoulder Questionnaire, ECG Electrocardiogram, ECHO Echocardiogram, CT Computed Tomography, VCUG Voiding Cysto-Urethrogram, PEDS QL Pediatric Quality of Life Inventory, CHQ Child Health Questionnaire, BIPQ Brief illness Perception Questionnaire, FPQ Frequency of Participation Questionnaire, PAQ Physical Activity Questionnaire, PROMIS Patient-Reported Outcomes Measurement Information System, SRBD Sleep-Related Breathing Disorder Scale, ESS Epworth Sleepiness Scale.

3.13.8 Standardisation of hypermobility measurement approaches

Whilst hypermobility screening assessments were the most commonly reported measurement approaches, evidence of standardisation was lacking. The Beighton score was most commonly used (93%, n=94), however only 12 studies reported evidence of standardisation (goniometry or standardised positioning).

Additionally, the cut-off points to determine hypermobility was not consistent to age or sex. Studies reported Beighton scores of ≥4 according to the Brighton and or Villefranche criteria at the time (116, 148, 157). A Beighton score of ≥6 was reported in other studies such as Fatoye et al., 2012 noting that as the Brighton criteria had yet to be validated in children, a Beighton score of ≥6 was considered as having HMS (150). Moore et al., 2019 screened specifically for generalised JH using the Beighton score cut-off ≥6 and was the sole study to clearly document use of a standardised protocol, using goniometry at the elbow, knee and 5th MCP (49) as per the protocol (54).

3.13.9 Clinical characteristics

Clinical characteristics were identified in empirical studies where specific characteristics were attributed to the study populations(n=108). Of the 108 studies, only those where clinical characteristics were clearly stratified by age (described in a priori developmental stages) were included (n=89) to answer the research questions.

In total n=4444 participants were included (children n=847; adolescents n=2553; young adults n=50; not specified n=994). Studies were scrutinised, but if data were not stratified according to one of the three developmental stages, it could not be included in the review. Primary data were analysed with respect to developmental stage and clinical domain. A summary of findings is presented in Figure 3.9.

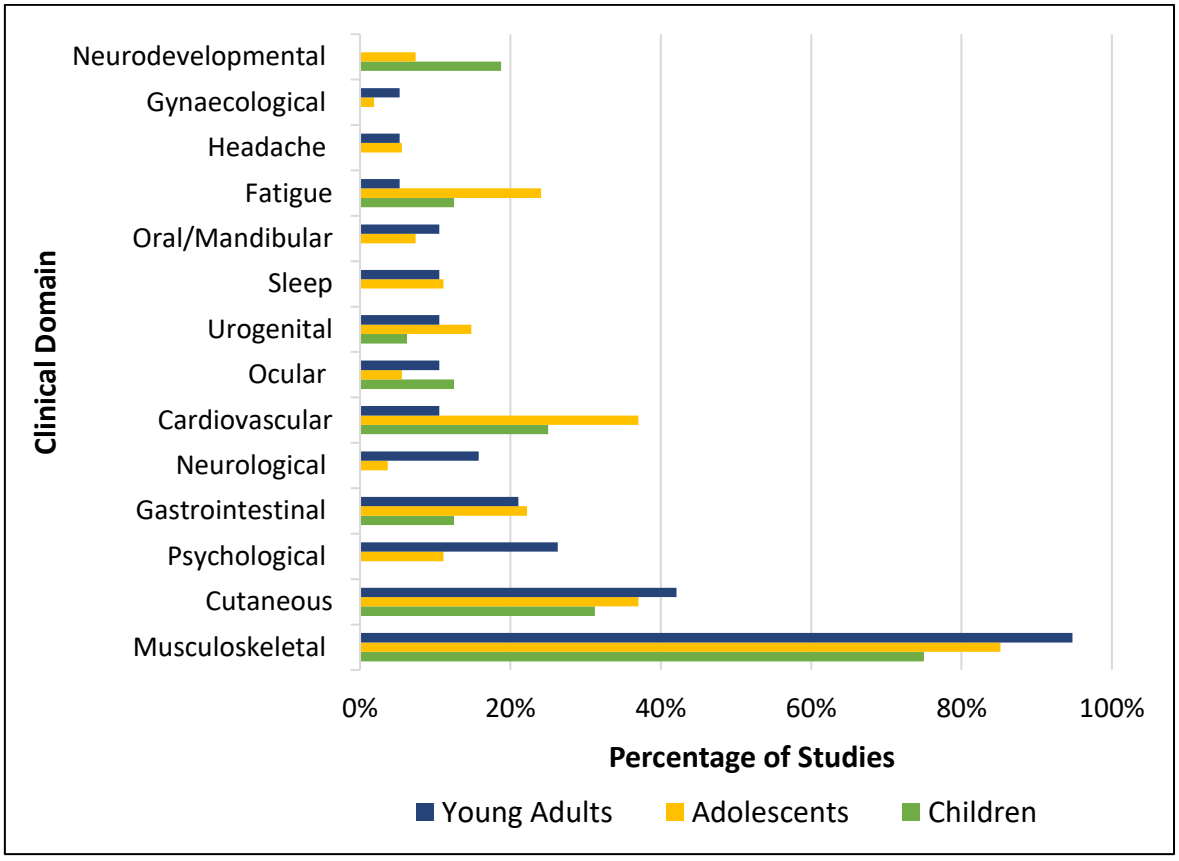


Figure 3.8 Percentage of studies reporting clinical characteristics in children, adolescents, and young adults in clinical domains identified in the scoping review

3.13.9.1 Childhood

Clinical characteristics in children were reported in 16 studies (21, 49, 66, 78, 86, 120, 129, 133, 137, 144, 158-163). Musculoskeletal complaints were reported in 75% (n=12) of these studies, including pain (21, 49, 86, 120, 161), exercise-induced pain (66), myalgia (144), and arthralgia (66).

Other characteristics included hyperextensible joints (129, 162), joint subluxations (129), reduced balance (49), low muscle tone (49), unstable gait (163), weakness (133), and decreased exercise capacity and participation in exercise compared to peers (133). Cutaneous features were reported in 31% (n=5) of studies. Reports included unusually soft or velvety skin (86, 120), skin extensibility (66, 129), and easy bruising (129). Three studies reported neurodevelopmental features including gross motor delay (86), co-ordination difficulties (21) or gross and fine motor, social and literacy problems (158).

Two studies reported cardiovascular clinical characteristics: aortic root dilatation and mitral valve prolapse (120, 144). Two studies reported fatigue (49, 86). One of these studies, a large retrospective review, found 89% of participants reported a 'sense of fatigue during or after activity' (86).

3.13.9.2 Adolescence

Clinical characteristics in adolescents were reported in 54 studies (85, 87, 106-108, 111-117, 121, 124-128, 132, 135, 140, 141, 143, 148-150, 153-155, 164-189). Musculoskeletal characteristics were reported in 85% (n=46) of studies and included, chronic recurrent pain (108, 128, 153, 164, 168, 170, 176, 177) and joint instability, sprains, and dislocations (108, 141, 153, 164, 170, 177). Clinical characteristics from the cardiovascular domain were reported in 37% (n=20) of studies, including valve prolapse and greater aortic root (140, 171) and dysautonomia including orthostatic intolerance (87, 116, 143, 148, 154, 155, 189). Cutaneous features were reported in 35% (n=20) of studies (85, 87, 116, 131, 137, 154, 155, 169, 174-176, 178, 179, 181, 184, 185, 190, 191) notably easy bruising (85, 87, 108, 155), hyperextensibility (135, 141, 171), soft velvety skin (169, 181), delayed wound healing, easy scarring (116, 169), and striae (174). Fatigue was reported in 24% (n=13) of papers/studies (114-116, 131, 148, 153-155, 170, 173, 177, 183, 189). Gastrointestinal characteristics were reported in 22%, n=12 (85, 114, 116, 145, 148, 155, 168-170, 177, 183, 189). Clinical characteristics included chronic gastritis (170), constipation (168), recurrent abdominal pain and chronic diarrhoea (116, 169) and vomiting (155). Urogenital features were reported in 15% (n=8) (85, 87, 141, 143, 148, 168, 183) including primary nocturnal enuresis and daytime symptoms of urinary urgency (141). Sleep disorders were reported in 11% (n=6) of studies (121, 155, 168, 173, 177, 183) including insomnia (121, 155), obstructive sleep apnoea, circadian rhythm disorders, periodic limb movement disorder, and hypersomnia (121, 173). Psychosocial features were reported in 11% (n=6) of studies (148, 150, 155, 164, 167, 177). Characteristics included anxiety and depression (148, 155, 164, 167, 177), and eating disorders (177). Neurodevelopmental characteristics were reported in 7% of studies (168-170, 183) including relatively higher rates of learning difficulties, dyslexia, and dyspraxia (168). Kindgren et al., 2021 reported a statistical association between neuropsychiatric conditions, such as Attention Deficit Hyperactivity Disorder (ADHD) and children

diagnosed with HDS and hEDS, by reviewing patient registry records of children aged 6-18 years treated in a Swedish paediatric and youth medicine clinic (183).

3.13.9.3 Young adulthood

Nineteen studies included participants between 20 and 24 years (123, 134, 142, 192-207). Musculoskeletal characteristics were reported in 95% (n=18) of studies, with the exception of one study, where features were screened, but no musculoskeletal features were reported (195). Characteristics included arthralgia (123, 134, 193, 196, 198, 204), joint instability, dislocation (123, 194, 201, 204) and reduced dynamic balance (192). Cutaneous features were reported in 42% (n=8) of studies (123, 193, 195-197, 199, 205, 206). Characteristics included easy bruising (193, 196), soft skin (205) and striae (206). Psychological features were reported in 26% (n=5) of studies (123, 134, 193, 203, 205) including depression (134, 205) and anxiety (123). Gastrointestinal characteristics were reported in 21% (n=4) of studies (123, 134, 193, 204). Two studies reported urogenital characteristics: stress incontinence and dysuria (134, 204).

3.14 Discussion

3.14.1 Overview

This is the first scoping review to explore the literature on children and young people with symptomatic hypermobility with a unique focus on developmental context. This review systematically clarified and interpreted the considerable quantity of diverse literature to make it more accessible to clinicians and researchers. Research on those with symptomatic hypermobility was more prolific in the last 12 years, extends over many different clinical domains, and consists largely of narrative reviews and case studies. The level of evidence of the literature on symptomatic hypermobility is predominantly of a lower hierarchy (119). Case reports and series may represent more extreme clinical cases but were included due to the objectives of this scoping review to explore the full extent of the literature. The Beighton score was the most commonly used tool to screen for hypermobility, but there were limited details regarding how it was used. Similarities and differences in the presenting clinical characteristics across the developmental stages were identified.

3.14.2 Clinical characteristics

This review found that musculoskeletal symptoms are the most prevalent clinical characteristics, and akin to cutaneous features, were reported across all developmental stages. Neurodevelopmental clinical characteristics were more common in children (21, 86, 168). In adolescents, dysautonomia, fatigue, sleep issues, and symptoms from urogenital and gastrointestinal domains were reported more frequently. Dysautonomia is also common in those with chronic functional pain conditions and might not be a primary indicator of symptomatic hypermobility (8, 114). The onset of puberty was found to be associated with a worsening of symptoms in only one study, although this data was based on recall of symptoms during puberty (208). On analysis of symptoms around the premenstrual period, symptoms could be alleviated by use of the contraceptive pill, suggesting the role of hormones on symptoms experienced by patients with symptomatic hypermobility (208). Of interest, psychological characteristics such as anxiety and depression were reported in over a quarter of all young adult studies (123, 134, 193, 203, 205).

3.14.3 Screening hypermobility

Despite the Beighton score being commonly used (n=94), evidence of reporting of standardisation (positioning or goniometry) was documented in only 12 studies. This affects our confidence interpreting prevalence of hypermobility across different studies. A further issue of concern is that different Beighton score cut-off points were used. A large UK population study (n=6,022) using a Beighton score cut-off point of 4/9 reported a high prevalence of hypermobility in girls (27.5%) and boys (10.6%) (50), while a study of Danish school children using a cut-off point of 6/9 resulted in a lower prevalence (9.4%) (78). A standardised Beighton protocol has been proposed and validated in school-aged children (54), and whilst other studies may have reported elements of standardisation, only one study reported using this protocol in school aged children (49). Barriers to its use may be a lack of awareness, equipment (goniometry), or time. However, in order to accurately assess joint hypermobility, to avoid over or under diagnosis, the utilisation of standardised tools using validated protocols in clinical practice and research is essential.

3.14.4 Other clinical domains

Seven different assessments of function, and 11 different assessments of motor control were identified in this review. Assessments to determine cutaneous features appear to be mostly subjective. There were six different types of cardiovascular assessments, including use of echocardiography, which was recently investigated in a retrospective chart review of paediatric patients with a diagnosis of some type of EDS (113). Authors report substantial use of echocardiography in patients with suspected hEDS but found that once other genetic conditions were ruled out, children with hEDS did not have significant aortic disease, and mitral valve prolapse occurred at the same incidence as the general population (113). The variety of reported assessments for children and young people with symptomatic hypermobility may reflect the growing awareness of clinicians regarding the spectrum of symptoms. However, it also reflects the lack of guidance and use of specific standardised outcome measures. Additionally, it limits comparisons between studies.

3.14.5 Changing phenotype with age

Previous studies have suggested that there is a changing phenotype, characterised by a progressive worsening from childhood to adulthood (91). One of only two longitudinal cohort studies identified in this review reported that an increased incidence of multisystem complaints was more predictive of functional decline (116). This ScR categorised clinical characteristics according to specific developmental stages, comprehensively reporting evidence of a changing clinical presentation. However, to advance our understanding of children and young people with symptomatic hypermobility, future well-designed case control and longitudinal cohort study designs are required to observe such clinical characteristics that develop and/or change with age, so that health care professionals will be able to offer them optimum care over their lifespan.

3.14.6 Limitations

Unlike systematic reviews, scoping reviews can be used when literature exhibits a heterogenous nature which is not as amenable to a systematic review (209). The broad systematic search strategy was conducted by an experienced librarian and guided by expert clinicians and research team members with expertise across clinical and research spheres. There was an attempt to reduce some of the methodological heterogeneity by scrutinising literature, in particular the definitions of diagnosed symptomatic hypermobility, to ensure that studies of children with asymptomatic hypermobility were not included. Extraction of data for participants who were ≤24yrs presented significant challenges in the review and there were studies whereby data could not be extracted, which could be seen as a limitation. Articles not in the English language were excluded as it was beyond the scope of this study to include studies in other languages, and this is acknowledged as a limitation.

3.15 Summary

This review presents a synthesis of the diverse research on symptomatic hypermobility in children and young people in a developmental context. Given the changing temporal pattern of symptoms, longitudinal studies and large case control studies are warranted to provide better understanding of symptomatic hypermobility in this population. Such studies should have bespoke criteria and use standardised assessment protocols so that findings from different studies can be compared and data can be pooled for analysis.

The comprehensive reporting of symptoms, extending beyond the musculoskeletal system into wide-ranging clinical domains presents the consideration of alternative care pathways for children and young people, whereby not all require referral to traditional settings of tertiary rheumatology and genetic clinics. With clearer guidance for health care professionals, patients with clinically relevant hypermobility could be recognised earlier and managed locally, to address the broad symptomatology with appropriate support. Those who require onward assessment and referral to tertiary services could be identified. This can only be achieved if clinicians in primary and community care are

guided regarding bespoke assessment and diagnostic criteria with a background knowledge of paediatric conditions which present similarly.

Study I Key Findings

- The literature on symptomatic hypermobility in children, adolescents and young people is diverse, spanning multiple clinical domains
- Evidence of a changing temporal pattern of symptoms was found across developmental stages
- The majority of included study designs are of a lower quality study design, longitudinal studies and large case control studies are warranted
- Over 75 different clinical measurements were identified, limiting comparison between studies, standardised measurements are needed
- Clinical characteristics were found to extend beyond the musculoskeletal system into wide-ranging clinical domains
- Wide-ranging clinical characteristics indicate a potential for alternative care pathways
- A generalist approach is needed to address broad symptomatology, followed by targeted onward referral as appropriate
- Clearer guidance is needed for clinicians to be able to recognise symptoms earlier

Chapter 4 Study II: An investigation of the clinical characteristics in children and adolescents with symptomatic hypermobility

4.1 Introduction

Study I of this thesis was a scoping review of the literature, and using a developmental framework, comprehensively reported the chronic musculoskeletal and systemic impairments, in children and young people, with symptomatic hypermobility. These impairments impact elements of functioning, disability, and health (20, 41). This broad, heterogenous symptomatology represents a consistent challenge to clinicians. Understanding the complex interactions between physical and psychosocial factors may help to gain a better understanding of symptomatic presentations, and to direct the development of more bespoke care pathways for the management of those with symptomatic hypermobility. This chapter presents the quantitative component (Study II) of this mixed methods research (Figure 4.1).

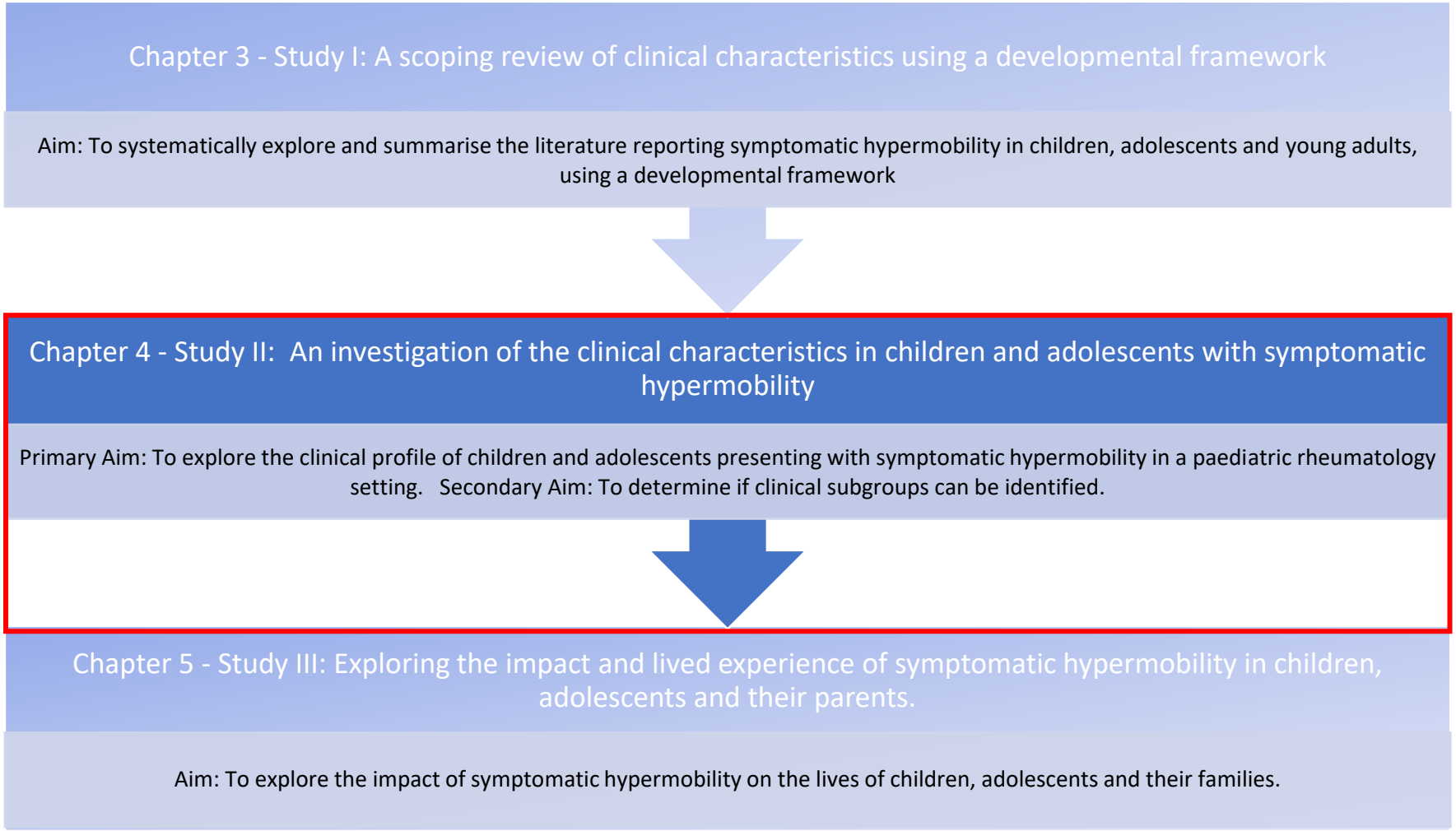


Figure 4.1 Outline of the studies in this thesis

4.1.1 Examining broad symptomatology

Throughout this thesis, the biopsychosocial framework has been used to help to provide insight into broader domains beyond biomedical to encompass all aspects of the biopsychosocial model (31). Assessing broad symptomology is a challenge to the clinician (210). As previously highlighted in Study I, there are many different measurement approaches used to assess patients with symptomatic hypermobility. Study I of this thesis, found that over 75 different measurement approaches were reported in the literature, for example, eight different hypermobility screening assessments and ten different methods of assessing pain. There is no agreed set of core outcome measures for use in paediatric symptomatic hypermobility (211). Measuring the four constructs of pain, function, quality of life and fatigue was recommended in a recent systematic review of outcome measures in children with symptomatic hypermobility (211). This review was based on a limited number of studies (n=6) which only focused on symptoms in the lower limb (211). Similar to Study I, the authors identified the considerable heterogeneity in the use of measurements (211). As the development of core outcome sets in paediatric symptomatic hypermobility is in its infancy, it is important to consider outcome measures in similar areas such as paediatric chronic pain. Efforts to develop core outcome sets in paediatric chronic pain have been ongoing for the past decade, most recently following more established engagement with patients, parents, and healthcare professionals (212). The following outcomes were recommended as mandatory; i) pain severity, ii) interference with daily living and iii) overall well-being, with consideration to including outcomes relating to emotional and physical functioning and sleep (212). As chronic pain is a common symptom in paediatric symptomatic hypermobility these recommendations merit consideration.

4.1.2 Clinical profiling

The development of comprehensive clinical profiles has been recommended in children and adults with symptomatic hypermobility in order to target their care (116). However, the clinical profiles of children and adolescents living in Ireland with symptomatic hypermobility are unknown. In Australia, a prospective longitudinal study in children with

symptomatic hypermobility (JHS/EDS-HT) found a high incidence of multi-systemic dysfunction and identified it to be the most important clinical factor associated with deterioration over time (116). Notably, it was found that the clinical profile of children most severely affected included the presence of stretch marks, orthostatic intolerance, diarrhoea, and urinary incontinence (116). They found that the presence of these multi-systemic symptoms predicted functional decline and suggested that clinicians should actively screen for such symptoms (116). Whilst pathological mechanisms remain unclear, screening multisystem complaints across clinical domains warrants clinical attention. Researchers and clinicians in primary or community care settings, may not have access to medical charts, and have reported difficulty assessing features such as pelvic and bladder dysfunction, finding them hard to quantify (49). Guidance is needed to identify the best methods of doing so, in settings outside of tertiary centres.

4.1.3 Clinical subgrouping

In the field of Medicine, clinical populations can be heterogenous, and better understanding of this heterogeneity may lead to more effective and targeted treatments, and direct care to better suit patient profiles (213). Classification helps us recognise and categorise subgroups (213). Numerical methods, such as cluster analysis, are used to derive classifications through the identification of subgroups in the data (213). The term 'subgroup' in this study is used to refer to a set of individuals within a population, with similar characteristics (214).

Identifying if there are subgroups to which patients can be allocated, is important as it will help clinicians to target treatment, which may optimise outcomes for these patients (20). Subgrouping approaches have been incorporated into the management of other heterogenous conditions such as low back pain (16) and patellofemoral pain (17). A low, medium and high-risk subgroup, driven by physical or psychosocial factors was determined by the development of a screening tool by researchers in Keele University in 2008, to provide a stratified approach to a matched pathway of intervention for non-specific low back pain, now widely used in clinical practice (16, 215). Three subgroups of patients with patellofemoral pain were identified based on six clinical assessment tests in

an exploratory study of 127 participants (17). A decision tree model, developed by the American Physical Therapy Association in their clinical practice guidelines for patellofemoral pain, incorporated the findings of impairment-based clusters to guide the management of patient with patellofemoral pain (216). Authors also highlighted the importance that intervention strategies often change during a patient's episode of care, and continual re-evaluation is important to provide optimal treatment (216).

4.1.4 Subgrouping in symptomatic hypermobility

Heterogenous clinical presentations in symptomatic hypermobility may limit treatment effectiveness, implying that treatment should be targeted to more homogenous clinical subgroups (20, 21, 217). The identification of clinical subgroups has been explored in two studies specific to children with symptomatic hypermobility (85, 86), with one further study exploring clusters of children, observed for 3 years in a longitudinal design (116). Pacey et al., 2015 identified five subgroups (joint affected, athletic, systemic, soft tissue and high BMI) in n = 89 children (85), Di Mattia et al., 2019 identified two subgroups (athletic-persistent and systematic-profound) from data extracted from case notes in n=318 children (86) and Scheper et al., 2017 identified three subgroups in terms of functional impairment (mildly affected, moderately affected and severely affected) in n = 101 children (116). Different methodologies were used and variations in populations, clinical variables, and data analysis mean that comparisons are limited, but these preliminary, exploratory studies provide a basis for further study and represent a move towards more targeted management.

4.1.5 Statistical methods used for identifying subgroups

Different statistical methods are used in research that aims to identify clusters of subtypes of patients, grouped according to specific clinical symptoms or presentations. Cluster analysis is a method whereby multiple variables (known as 'features') are used to identify clusters or subgroups in the data (218). Other methods for identifying subgroups such as latent class analysis (categorical data) and latent profile analysis (quantitative

data) (86) can also be used to estimate the probability of membership of latent (or unknown) subgroups, based on a set of variables (17). Hierarchal clustering is a type of cluster analysis. It separates the individuals into groups, by a series of partitions, which are progressively subdivided in an agglomerative method (213). There are similarities to these statistical methods, however they make different assumptions, use different statistical procedures and different types of features (219). For example, latent class analysis uses categorical variables as the input, whereas cluster analysis uses variable means to define the nearness of cases, therefore the variables (features) are continuous (219).

Hierarchal clustering was chosen for this study as it incorporates an approach not dissimilar to clinical reasoning in clinical practice, where scores are assessed in sequence to build up a clinical profile. This bottom-up approach places participants into subgroups based on similarity or distance, of the chosen features (clinical tests). The clusters can then be visually represented on a dendrogram or tree diagram (213). When using this method, attention to the scaling and encoding of features, choice of cluster analysis method, and evaluating the quality of the cluster results are important recommendations (218).

4.1.6 Targeted treatment model

Although lacking evidence in the literature, some clinical centres appear to have moved towards tailored treatment approaches, as detailed in a position statement from GoodHope EDS clinic at the Toronto General Hospital (220). This tertiary clinic utilises a multidisciplinary pathway approach, where they provide a '1-stop interdisciplinary model of health care' for adults with EDS including HSD/hEDS (220). The EDS clinic details two specific exercise rehabilitation pathways: i) rehabilitation and ii) conditioning exercise (220). Entry into the appropriate exercise and rehabilitation pathway is assessed using a site-specific scale, based on an assessment of the level of impairment and interference (Figure 4.2) (220).

Score	Description
0	Able to participate in all self-care, occupational and leisure activities and exercise without restriction
1	Able to participate in self-care activities as well as activities requiring light to moderate exertion, unable to perform or difficulty with physically strenuous activities
2	Able to participate in self-care activities but unable to perform or difficulty with occupational and leisure activities of mild or moderate exertion
3	Unable to perform some self-care activities and/or require assistance with others limited activities beyond the bed or chair most of the time
4	Unable to perform all self-care activities, not ambulatory

Figure 4.2 GoodHope EDS impairment and Interference Scale (GEISS). Source (173)

More functionally restricted patients start with physical rehabilitation (GEISS 2-3), whereas more highly functioning patients (GEISS 0-1 or 1-2) engage in a general conditioning and fitness programme (220). Alternatively, clinical pathways to subspecialities such as pain, gastrointestinal, psychology, social work, immunology, cardiology, neurology, neurosurgery and respiratory are also built into the overall interdisciplinary patient service flow model of care (220).

Research has yet to establish whether treatment within such allocated pathways and groupings, will lead to improvements in patient outcomes, and is the best use of resources.

4.1.7 Research questions

1. What are the clinical characteristics of children and adolescents with symptomatic hypermobility?
2. Can children and adolescents with symptomatic hypermobility be assigned to clinical subgroups based on clinical assessments?

4.1.8 Primary and secondary aims of Study II

The primary aim of this quantitative component of this mixed methods study was to explore the clinical profile of children and adolescents presenting with symptomatic hypermobility in a paediatric rheumatology setting. The secondary aim was to determine if clinical subgroups could be identified.

4.1.9 Objectives

1. To examine the feasibility of conducting a testing protocol on children and adolescents
2. To define the clinical characteristics of children and adolescents with a diagnosis of symptomatic hypermobility.
3. To identify if clinically disparate subgroups can be formed
4. If subgroups can be formed, to explore how the subgroups differ, and examine the associations with age, biological sex, and other factors such as multi-systemic complaints.

4.2 Methods

4.2.1 Study design and setting

This study was an observational cross-sectional study. This allowed for the assessment of multiple outcomes at one time point. The cross-sectional design meant that participants and their families were not required to travel over numerous time points to attend further research assessments. This was time efficient and reduced the burden on parents and participants. The setting for this study was a tertiary children's hospital. Specifically, the setting was the National Centre for Paediatric Rheumatology (NCPR) within a tertiary children's hospital across three sites. The testing took place in each of the three clinical sites which are located in different parts of Dublin, Ireland. The feasibility study took place between January and March 2021 (see Section 4.4). The STROBE guidelines for the reporting of observational studies were followed (Appendix 6) (25).

4.2.2 Ethics approval

Ethics approval was sought from Children's Health Ireland Ethics (Medical Research) Committee. Ethics approval was granted (Ref: GEN/740/19 (Appendix 7) prior to the awarding of a National Children's Research Centre (NCRC) Clinical Fellowship (Grant code D/19/5) (Appendix 8). Ethics approval was also sought from Trinity College Dublin Faculty of Health Sciences Research Ethics Committee (Ref: 201002) (Appendix 9). Mandatory Data Protection Impact Assessments (DPIAs) were also required from each site's Data Protection Officer (DPO) and approved (Appendix 10 & 11). A joint controller agreement between academic and clinical sites was sought and approved (Appendix 12).

4.2.2.1 Additional ethics approvals

Additional ethics and data protection applications were required as a consequence of the significant changes to clinical services following the COVID-19 pandemic. An amendment was granted by the Children's Health Ireland Ethics (Medical Research) Committee (Ref: GEN/740/19) (Appendix 7).

4.2.2.2 Response to new GDPR regulations

Two co-supervisors of this thesis are working in UK Universities which were deemed third parties in relation to data protection (Data Protection Act 2018 (221)) . Appropriate Data Transfer Agreements were drafted with input from the Principal Investigator, supervisors, academic DPO and legal departments in TCD, along with correspondence with the appropriate Universities (Appendix 13). See Figure 4.3 for a timeline for the ethics approvals, data protection agreements and transfer agreements for this thesis.

Figure 4.3 Timeline of ethics approval and data protection and transfers agreements. CHI Children's Health Ireland, GDPR General Data Protection Regulation, TCD Trinity College Dublin, DPO Data Protection Officer, DPIA Data Protection Impact Assessment

4.2.3 Participants

All patients diagnosed with symptomatic hypermobility presenting to tertiary paediatric rheumatology clinics (public and private consultant clinics and physiotherapy triage clinic) during the time period from July 2021 to January 2023 who fulfilled the inclusion/exclusion criteria were eligible for inclusion in the study. As the study was conducted in the National Centre for Paediatric Rheumatology in Ireland, participants were representative of all locations in Ireland.

4.2.3.1 Inclusion criteria

1. Children and adolescents aged 6-16 years old
2. Attending the paediatric rheumatology service in a tertiary children's hospital

3. Diagnosis of symptomatic hypermobility (inclusive of both Hypermobility Spectrum Disorder (HSD) or hypermobile Ehlers-Danlos syndrome (hEDS)).

4.2.3.2 Exclusion criteria

1. Diagnosis of inflammatory disease
2. Trauma or surgery unrelated to symptomatic hypermobility that affected the ability to undertake the objective testing.
3. Any other significant co-morbidities that affected the ability to participate in the objective testing.

4.2.4 Recruitment

The study was advertised using a poster on notice boards and flyers in the clinical waiting areas (Appendix 14) of the National Centre for Paediatric Rheumatology clinics across three clinical sites. Participants were screened for eligibility by the Consultant Paediatric Rheumatologists and/or the Clinical Specialist Triage Physiotherapist. If the parents were interested in their child/adolescent participating in the study and/or wanted further information, they were advised to contact the Principal Investigator. If contacted, the Principal Investigator sent the parent/guardian participant information leaflet (PIL) (Appendix 15) and an age appropriate PIL for the child/adolescent (Appendix 16) via post or email. The PIL contained detailed information about the study and assured parents that they and their child/adolescent were under no obligation to participate. Explicit informed consent and assent were sought prior to participation in the study (Appendix 15 & 16). After the reflective period the Primary Investigator contacted the parents/guardians and child/adolescent to address any queries and to confirm if they were interested in taking part in the study and to schedule an appointment for testing. The Principal Investigator obtained written informed assent and consent from each participant and their parent/guardian respectively at the meeting/assessment. If they met the inclusion criteria and had no criteria for exclusion, they were enrolled in the study. See Figure 4.4 for a flow chart of the recruitment process.

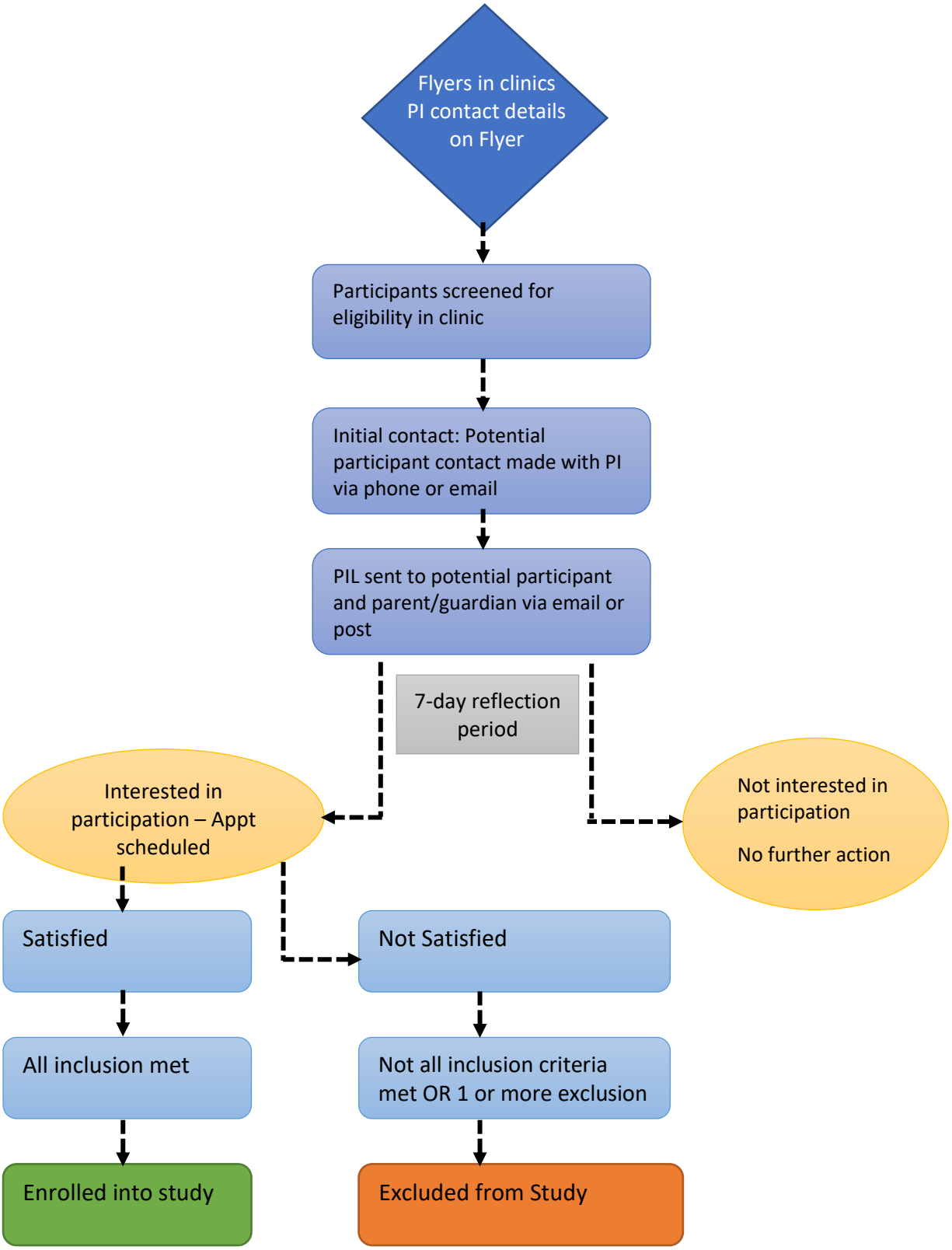


Figure 4.4 Participant recruitment flow chart

4.2.5 Study procedures

In light of the lack of a core outcome set, and current heterogeneity reported in the literature, a broad comprehensive approach was taken to the selection of clinical measurements used in the study. Subjective and objective measures, that were valid and reliable in a paediatric setting, and which could be carried out in a typical clinical environment were selected (116, 222). This was to facilitate the translation of research into clinical practice. Attention to measures identified in Study I, as well as previous studies exploring clinical characteristics in similar cohorts (49, 85, 86, 116), liaison with expert clinicians and this thesis' supervisory team informed the selection. A structured interview and medical chart review were included to screen multi-system complaints and extra-articular features and explore other factors beyond biological factors, such as school attendance, and current management.

The standardised assessment of each participant had four distinct stages including:

i) reviewing the medical chart/electronic health record of the child/adolescent participants,
ii) child/adolescent report and parent proxy-report subjective questionnaires
iii) conducting a structured interview and
iv) carrying out objective clinical measurements.

The testing took place in the tertiary children's hospital across three clinical sites. The same, experienced chartered physiotherapist (Principal Investigator) undertook all testing with a parent or guardian present. The Principal Investigator has extensive paediatric experience in carrying out medical chart review, structured interviewing and carrying out the clinical measures with parents, children, and adolescents. The testing was non-invasive, and it took ninety minutes in total to carry out the testing (excluding the medical chart/electronic health record review), allowing for breaks between tests as required.

4.2.5.1 Medical chart review

The participant's medical chart/electronic health record (EHR) was reviewed. The following information was obtained: age, biological sex, diagnosis, additional diagnoses, medication/s and multi-systemic involvement (Table 4.1).

4.2.5.2 Subjective clinical measurements

The clinical measurements were selected based on a review of the evidence in Study I of this thesis and clinician and researcher expertise. Four questionnaires were used in this study as follows: i) PedsQL™ 4.0 Generic Core Scale (223); ii) Paediatric Pain Questionnaire (224); iii) PedsQL™ Multidimensional Fatigue Scale (225) and iv) Physical Activity Questionnaire (226). Each questionnaire is described in more detail in section 4.2.6.

4.2.5.3 Structured interview

A structured interview took place with the child/adolescent and their parent following the questionnaires, to ascertain further clinical information. The following information was obtained from the structured interview: additional diagnosis/es, medication/s, presenting symptom/s at onset, event prior to initial onset of symptom/s, association with ongoing symptom/s, multi-systemic complaints, length of time and location of perceived diagnosis, number of chronically painful joints, number and location of perceived subluxed or dislocated joints, subsequent attendance at accident and emergency and subsequent investigation of perceived subluxed/dislocated joints, whether the participant was attending physiotherapy, ethnicity and type of current schooling and engagement (Table 4.1). Questions were directed to both the child/adolescent and parent as appropriate to the age and developmental stage of the child/adolescent. Data were recorded on the Medical Chart & Structured Interview Record Sheet (Appendix 17). Information reported in the structured interview was compared and where possible, verified in the participant's medical chart, Table 4.1 provides a record of when this was the case.

Table 4.1 Description of variables and rationale for inclusion of data collected by medical chart review and structured interview

Variable	Source	Description	Rationale
Age	Medical Chart	Age in years and months	Inclusion criteria for study
Biological Sex	Medical Chart	Sex assigned at birth	For comparison within groups
Diagnosis	Medical Chart	Term used for diagnosis	Inclusion criteria for study
Additional Diagnoses	Structured Interview & Medical Chart	List of additional diagnoses	For comparison within groups
Medication/s	Structured Interview & Medical Chart	Current medications	For comparison within groups
Presenting symptoms at onset	Structured Interview	Presenting symptoms at onset as perceived by participants	For comparison within groups
Event prior to initial onset of symptom/s	Structured Interview	Any event reports prior to the onset of symptoms categorised as injury/virus/other	For comparison within groups
Associations with ongoing symptoms	Structured Interview	Any association reported by the participants understood to be related to ongoing symptoms	For comparison within groups
Multisystem complaints (skin, eyes, cardiovascular,	Structured Interview & Medical Chart	Reported multisystem complaints	For comparison within groups

gastrointestinal, urinary, headache, other)			
Length of time to perceived diagnosis	Structured Interview	Length of time (months) perceived since onset of symptoms to diagnosis as understood by the participant	For comparison within groups
Location where diagnosis was perceived to have occurred	Structured Interview	Health setting location of perceived diagnosis	For comparison within groups
Type current schooling	Structured Interview	In-school/home-school	For comparison within groups
% time engaged in schooling in the past 12 months	Structured Interview	Percentage of time engaged in schooling as perceived by the participant in the last 12 months	Covid-19 involved both in-school and home-schooling, therefore the term engagement was used in place of attendance
Number of chronically painful joints	Structured Interview	Number of painful joints greater than 3 months duration	For comparison within groups
Number and location of perceived subluxed or dislocated (joint instability) joint/s in the past 3 months	Structured Interview	Number and location of joint instability perceived as dislocation or subluxation in the last 3 months	For comparison within groups

A and E attendance due to joint instability episode	Structured Interview	In the presence of reported instability, document yes/no if there was a subsequent attendance to A and E due to the instability episode	For comparison within groups
Type of investigation due to joint instability episode	Structured Interview	In the presence of reported instability, document type of investigation due to the instability episode	For comparison within groups
Overall physiotherapy management in past year yes/no	Structured Interview	Document physiotherapy management within the last 12 months	For comparison within groups
Ethnicity	Structured Interview	As per Central Statistics Office Ireland	For comparison within groups

4.2.5.4 Objective clinical measurements

The clinical measurements were selected based on the findings of Study I of this thesis and clinician and researcher expertise. The objective clinical measurements used in this study consisted of nine objective tests (Table 4.2). The nine objective tests were as follows: i) Six-minute walk test (227); ii) Y-Balance Test (228); iii) Lower Limb Assessment Scale (56); iv) Straight leg-lift (229); v) Knee Extension Angle Test (52); vi) Beighton score (54); vii) Foot Posture Index (230); viii) Jamar Handheld Dynamometer (231) and ix) Bruininks-Oseretsky Test of Motor Proficiency Brief (232). Each test is described in more detail below. The results of the nine objective tests were recorded on the Clinical Data Collection Sheet (Appendix 18). Table 4.2 lists the four subjective and nine objective clinical measurements and variables assessed in Study II.

Table 4.2 Summary of subjective and objective clinical measurements and variables assessed in Study II

	Measurement	**Variable**
Subjective clinical measures	PedsQL™ 4.0 Generic Core Scale	Child and Parent-proxy self-reported Quality of Life
	Paediatric Pain Questionnaire	Child and Parent-proxy self-reported pain
	PedsQL™ Multidimensional Fatigue Scale	Child and Parent-proxy self-reported fatigue
	Physical Activity Questionnaire	Child self-reported physical activity
Anthropometrics	Anthropometrics	Height, weight, leg length
Obejctive clinical measures	Six-minute walk test	Functional capacity
	Y-Balance Test	Dynamic balance
	Lower Limb Assessment Scale	Hypermobility
	Straight leg-lift	Muscle endurance
	Knee Extension Angle Test	Muscle length
	Beighton score	Hypermobility
	Foot Posture Index	Foot posture
	Jamar Handheld Dynamometer	Grip strength
	Bruininks-Oseretsky Test of Motor Proficiency Brief	Motor skills

4.2.6 Subjective clinical measures

The child and parent questionnaires were used to obtain subjective information. This included information about quality of life, pain, fatigue, and physical activity levels. Three questionnaires were completed by both parent and child/adolescent (Quality of Life, Pain, and Fatigue). The Physical Activity Questionnaire was completed by the child/adolescent only. The child/adolescent and parent completed their questionnaires in

the same testing environment but were encouraged to complete their forms independently with the child/adolescent facing away from the parent where possible, and to discuss the questionnaires only on completion. This allowed for the child/adolescent and parent to consider their own responses, describing how they felt independent of each other.

4.2.6.1 Quality of Life

Quality of life was assessed using the PedsQL™ 4.0 Generic Core Scale (Paediatric Quality of Life Inventory) (Appendix 19). The PedsQL™ 4.0 Generic Core Scale measures Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items) and School Functioning (5 items) (223). It has demonstrated excellent reliability (233) in a paediatric rheumatology population and found to be valid (223) when distinguishing between healthy children and children with chronic health conditions. There are different versions of the PedsQL™ 4.0 Generic Core Scale for different age groups (2-4 toddler, 5-7 young child, 8-12 child and 13-18 adolescent), the items of each form differ only in developmentally appropriate language. There is a large database of the PedsQL™ 4.0 Generic Core Scales in healthy children and children with chronic health conditions including symptomatic hypermobility, that allows for comparisons between populations (87, 223). It has also been used by two physiotherapy-led research studies in cancer survivors, and children with cardiac conditions, in the same tertiary setting in Ireland (234, 235), allowing for comparison of children with different clinical presentations. Cut-off scores have been established as scores which fall 1SD below the population sample mean representing an at-risk status for impaired health-related quality of life (223). For this study child self-reported HRQOL scores were categorised a priori as 'at-risk' if Total score <69.71; Physical Health <72.98; Psychosocial Health <66.03 (parent-proxy Total score 65.42; Physical Health <63.28; Psychosocial Health <64.38) based on healthy populations PedsQL™ 4.0 questionnaire scores (223). Standardised procedures were followed as per the testing protocol (Appendix 20).

Scoring: Items were scored on a 5-point Likert scale 0 (never) to 5 (almost always). Younger children (ages 5-7 years) completed a 3-point scale child report (0= not at all a

problem; 2=sometimes a problem; 4 = a lot of a problem) with each response attached to a happy to sad faces scale. Scores were then transformed on a scale from 0 to 100 as follows: 0=100, 1=75, 2=50,3=25,4=0. The Physical Health Summary Score is the Physical functioning subscale (8 items). The Psychosocial Health Summary Score is created by the sum of the items in the Emotional, Social and School Functioning Subscales divided by the number of items answered (223). The Total score was the sum of all the items over the number of items answered on all the scales. Higher scores indicate better quality of life.

4.2.6.2 Pain

Pain was assessed using the PedsQL™ Paediatric Pain Questionnaire (Appendix 21). The PedsQL™ Paediatric Pain Questionnaire is a validated (236) pain questionnaire (224). commonly used in paediatric rheumatology settings to assess pain intensity and location for children and adolescents with chronic or recurrent pain (224). Child, parent and clinician responses were found to be reliable raters of current and worse pain (224). It has two parts, a visual analogue scale (VAS) 10-cm horizontal line, with descriptors “not hurting” or “no pain” and “hurting a whole lot” or “severe pain” and a gender-neutral body outline to describe location of pain with words to assess pain qualities (none, mild, moderate, severe) (237). For this study the following pain severity cut-off scores were used: mild 0-3; moderate 4-6; and severe 7-10. Standardised procedures were followed as per the testing protocol (Appendix 20).

Scoring: The number, location and severity of pain sites was documented by the Principal Investigator. A standard ruler was used to measure the VAS score of pain intensity.

4.2.6.3 Fatigue

Fatigue was assessed with the PedsQL™ Multidimensional Fatigue Scale (Appendix 22). This is an 18-item scale to measure child and parent perceptions of general fatigue, sleep/rest fatigue and cognitive fatigue in paediatric patients (225). It has been found to be reliable and valid in paediatric rheumatology settings including children and adolescents with inflammatory and non-inflammatory conditions (225). It comprises

child self-report and parent proxy-report forms to assess the parents' perception of their child's fatigue (225). The construct of fatigue is also recommended to be included in a future core outcome set in symptomatic paediatric hypermobility (211). Standardised procedures were followed as per the testing protocol (Appendix 20).

Scoring: The scoring of the PedsQL™ Multidimensional Fatigue Scale is identical to the PedsQL™ 4.0 Generic Core Scale, whereby items were scored on a 5-point Likert scale 0 (never) to 5 (almost always). There was a 3-point scale for the Young Child report (ages 5-7 years). Scores were then transformed on a scale from 0 to 100 as follows: 0=100, 1=75, 2=50,3=25,4=0. The total score was the sum of all the items over the number of items answered on all the scales. Higher PedsQL Multidimensional Fatigue Scale scores indicate fewer symptoms of fatigue, whereas scores nearer 0 indicate more fatigue.

4.2.6.4 Physical activity

Physical activity was assessed using the Physical Activity Questionnaire (PAQ) (226) (Appendix 23). The PAQ is a standardised, self-administered, 7-day recall instrument, with acceptable reliability (238) and validity (239). The PAQ was designed in Canada and therefore some of the sports are not relevant in a local Irish context. The current study used a questionnaire that was modified for the local population. These changes were as follows: 'recess' to 'break or yard', and Canadian sports to Irish sports: ice-skating, cross-country skiing and ice hockey were changed to Gaelic football, hurling/camogie, gymnastics, and rugby. Changes were similar to Voss et al., 2013 [156], and Condon et al., 2015 [157], who adapted the questionnaire for UK and Irish cohorts respectively. The choice of sports was based on the Principal Investigator's own expert opinion working in paediatrics for over 15 years with guidance from colleagues working in paediatric physiotherapy, and liaison with parents. The liaison with parents was achieved using an informal communication with a previously established group of parents of which I was already a member. This group was chosen as it included parents with children who were representative of each of the difference types of schools primary, secondary, private, public and including the different religious organisations including non-denominational. This was carried out to ensure that a thorough list of sports that were representative of

all types of schools was included in the Physical Activity Questionnaire Child and Adolescent (PAQ-C and PAQ-A). There was also a section on the questionnaire for 'other' sports, so this list did not have to be exhaustive.

The PAQ provides a summary physical activity score which can be converted into a nominal value, when compared to similar cohort normative values. PAQ scores of 2.9 for males, and 2.7 for females were identified as cut-off points to categorize UK children as 'sufficiently active' (240), and a similar study reported that the PAQ questionnaire could be used to discriminate between active and sedentary adolescents using a cut-off of 2.75 (241). There are two versions of this questionnaire, one for children (PAQ-C) approximately 8-14 years and one for adolescents (PAQ-A) approximately aged 14-19 years (238).

Physical Activity Questionnaire-Child (PAQ-C)

The PAQ-C was developed to assess general levels of physical activity for students in grades 4 to 8 and approximately 8 to 14 years of age. Although the PAQ-C has not been validated on children who are less than 8 years, the PAQ protocol allows for assistance from the Principal Investigator to read to younger children and the questionnaire has been used in a similar age cohort in an Irish study (242). In this study we used this for children in Irish national or primary level, approximately ages 6 to 13 years as adolescents attending secondary school were less likely to have 'recess' or its equivalent 'yard' as referred to in an Irish setting. Standardised procedures were followed as per the testing protocol (Appendix 20).

Scoring: The scoring for item 1 of the PAQ-C is a composite score, which was found by calculating the mean of all activities ("no" activity = 1, "7 times or more" = 5) on the activity checklist. For items 2 to 8 on the PAQ-C, the answers for each item start from the lowest activity response is 1 and progress to the highest activity response which is 5. Scoring for item 9, the mean of all the days of the week ("none" = 1, "very often" = 5) were taken to form a composite score. The final PAQ-C activity summary score was calculated as the mean of the 9 items. A score of 1 indicates low physical activity, whereas a score of 5 indicates high physical activity.

Physical Activity Questionnaire-Adolescent (PAQ-A)

The PAQ-A is very similar to the PAC-C but removes the term 'recess'. It was developed to assess general levels of physical activity for high school students in grades 9 to 12 and approximately 14 to 19 years of age. In this study, this was used for adolescents attending Irish secondary level schools, approximately ages 13 to 16 years. Standardised procedures were followed as per the testing protocol (Appendix 20).

Scoring: The scoring for the PAQ-A item 1 is a composite score found by calculating the mean of all activities ("no" activity = 1, "7 times or more" = 5) on the activity checklist. For items 2 to 7 on the PAQ-A, the answers for each item start from the lowest activity response which is 1 and progress to the highest activity response which is 5. Item 8 score was calculated as the mean score for each day of the week ("none" = 1, "very often" = 5). The final activity summary score was calculated as the mean of the 8 PAQ-A items. A score of 1 indicates low physical activity, whereas a score of 5 indicates high physical activity.

4.2.7 Anthropometrics

The procedures for measuring height and weight were adapted from the UK National Child Measurement Programme: operational guidance (243). Anthropometric results were recorded on the Clinical Data Collection Sheet (Appendix 18).

4.2.7.1 Height

Height in barefoot was measured with a stadiometer, Seca 213 portable height stand (Seca, Hamburg Germany). Standardised procedures were followed (Appendix 20).

4.2.7.2 Weight

Weight was measured with a Seca 877 electronic weighing scales (Seca, Hamburg Germany). Standardised procedures were followed (Appendix 20).

4.2.7.3 Body Mass Index (BMI)

BMI Percentile was calculated using the participant's biological sex and age in years and months using the Centre for Disease Control and Prevention BMI calculator Child and Teen (244). The participant's BMI was classified according to the Centre for Disease Control (CDC) classification of BMI-for-age (Table 4.3).

Table 4.3 BMI centile category (194)

BMI centile categories for age	
Underweight	Less than 5th percentile
Healthy weight	5th percentile to 85th percentile
Overweight	85th to >95th percentile
Obese	95th percentile or greater

4.2.7.4 Leg length

The length of the participants lower limb was required, so that the YBT reach distances could be normalised to participant leg length. This allowed for comparison among studies. A standardised procedure was followed (Appendix 20).

4.2.8 Objective tests

4.2.8.1 Functional capacity

Function is included as one of four constructs recommended to be in a future core outcome set in symptomatic paediatric hypermobility (211). In this study, functional capacity was assessed using the six-minute walk test (6MWT), which has been shown to be safe, reliable and valid in healthy (245, 246), and unhealthy individuals including children with chronic disease (247). The 6MWT was conducted according to the American Thoracic Society (ATS) guidelines (227). The primary outcome measured was the distance walked in 6 minutes (6MWD) rounding to the nearest meter. Oxygen saturations are usually recorded for patients with respiratory disease, but this was unnecessary for patients included in this study and was not assessed. The modified Borg scale (Appendix

24) was used to assess the participant's perceived rate of exertions, as per the ATS guidelines (227). Perceived level of breathlessness was recorded at the beginning and at the end of the exercise by asking the participant to grade their breathing level according to the scale, printed out on heavy paper in 20-point font size according to ATS protocol, 2002 (227). A "warm-up" period before the test was not performed as per the ATS guidelines (227). Data were normalised to age and sex (248). Standardised procedures were followed according to the ATS guidelines (227), as per the testing protocol (Appendix 20).

Figure 4.5 Participant during a test lap of the 6MWT where the participant was asked to walk continuously for six minutes along a 30m marked corridor at a self-selected pace

4.2.8.2 Dynamic balance

Dynamic balance was assessed using the Y Balance Test (Y Balance Test Kit Sports Physio Supplies Ltd. 210-158) (Figure 4.6). The Y Balance Test (YBT) is a dynamic balance test developed from the Star Excursion Balance Test (SEBT) (245). The YBT is a shorter version of the SEBT incorporating reaching in 3 different directions, Anterior, Posteromedial and Posterolateral whilst maintaining stance on one foot (Figure 4.7) (228).

The YBT has good to excellent reliability when using the standardised equipment and methods detailed in the protocol (228). For the purposes of this research, the standardised protocol originally described by Plisky et al. 2009 was strictly followed but the modification of language was used for children younger than 8 (or as determined by

the Principal Investigator), to maintain the interest of the younger children (228, 249). The YBT has been found to be a feasible and reliable assessment of dynamic balance in healthy children (249).

Standardised procedures were followed as detailed in the protocol (Appendix 20). A short video demonstrating the YBT (Samsung Galaxy Tab A8) was shown to the participants before conducting the testing (Appendix 25). Participants conducted the YBT following the six-minute walk test, which acted as a warmup.

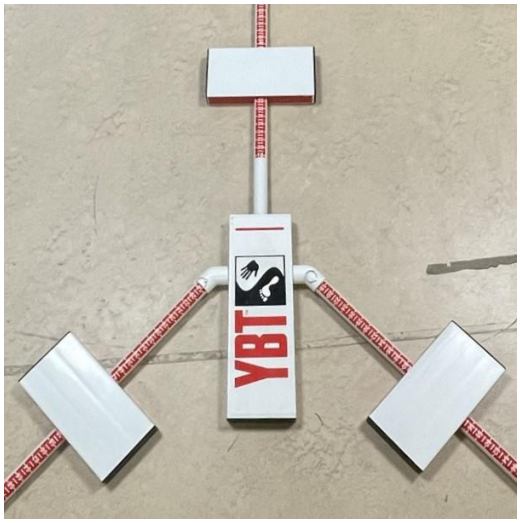
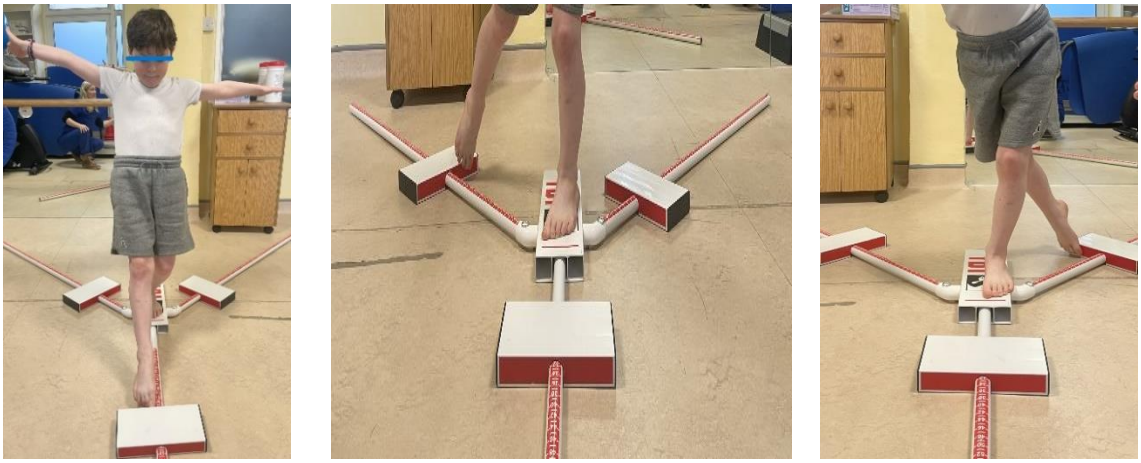


Figure 4.6 Y Balance Test Kit



a **b** **c**

Figure 4.7 a, b, c. Performance on the Y balance test in the Anterior (a), Posteromedial (b) and Posterolateral (c) directions

Scoring: The reach distance (cm) was recorded in Microsoft Excel (Microsoft Corporation, Microsoft Excel, 2018), and used to calculate the normalised reach distance as follows: normalised reach distance = reach distance / leg length x 100. The composite reach distance was calculated as follows: Composite reach distance = (normalised anterior reach distance + normalised posteromedial reach distance + normalised posterolateral reach distance / 3.

4.2.8.3 Hypermobility

Two tools were used to screen for generalised hypermobility in participants. The Lower Limb Assessment Scale (LLAS) and the Beighton score (BS) (46, 56). Currently no tool has been found to be the 'best' assessment to classify generalised hypermobility (53). The BS is commonly used in clinical practice, is quick and easy to use, and has good reliability (53). The LLAS was developed for children, and more recently validated for use in adults (56, 57). It focuses on multidirectional hypermobility and joint laxity and uses more advanced musculoskeletal assessment methods used by therapists including physiotherapists, podiatrists and rheumatologists (56). The BS focuses more on upper limb hypermobility and the LLAS focuses exclusively on lower limb hypermobility including the ankle joint which is commonly symptomatic in children and are not included in the BS (168). In this study, the two hypermobility screening tools are described in the order of testing.

The Lower Limb Assessment Scale

Generalised joint hypermobility was first screened using The Lower Limb Assessment Scale (LLAS) (Appendix 26) (56). The standardised protocol reported by Ferrari et al. (56) was followed for this study. The LLAS has been found to be valid and reliable in a school aged population aged 5-16 years in children (62) (57). This assessment comprises movements of the joint in several planes of motion, and the movements are typical of those used in clinical practice, including movements used by physiotherapists (56). There are 12 items in the test and a cut-off score of ≥7/12 is used to determine presence of hypermobility in the lower limbs. Standardised procedures were followed as detailed in the protocol (Appendix 20).

Scoring: Each positive test was awarded one mark, a total of score of 12 marks for each leg was available (56).

The Beighton Score

Generalised joint hypermobility was also screened using the Beighton score (BS). The Beighton score is calculated using the standardised Beighton protocol (54) and is valid in primary school aged children (54). The BS is made up of five movements, four of which are passive, and one is active (Figures 4.8 – 4.11). Standardised procedures were followed as detailed in the protocol (Appendix 20).

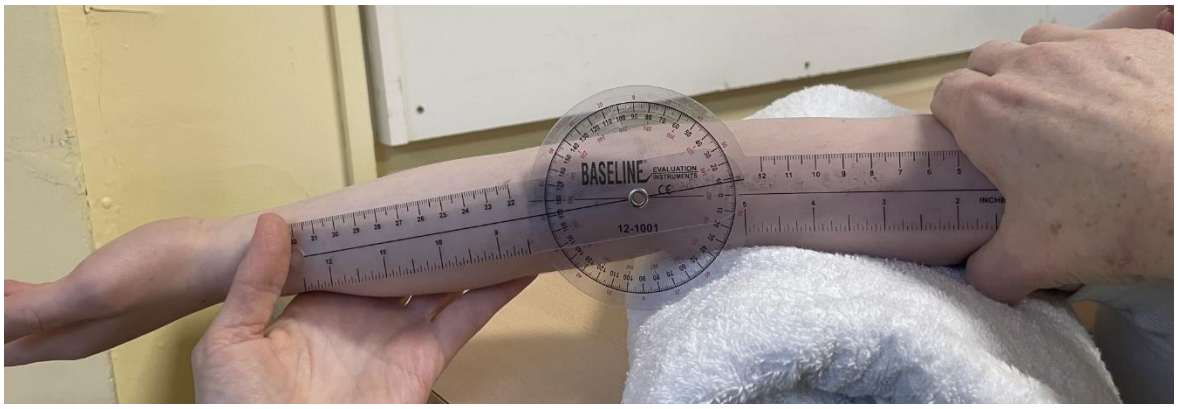
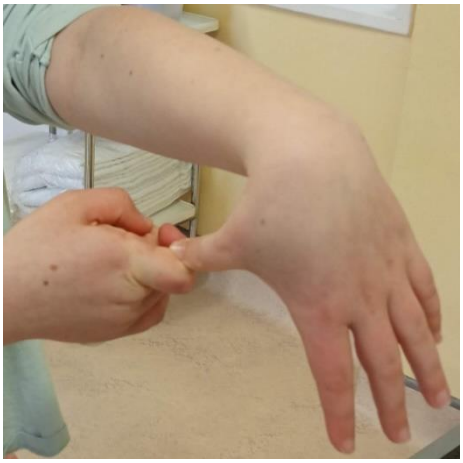
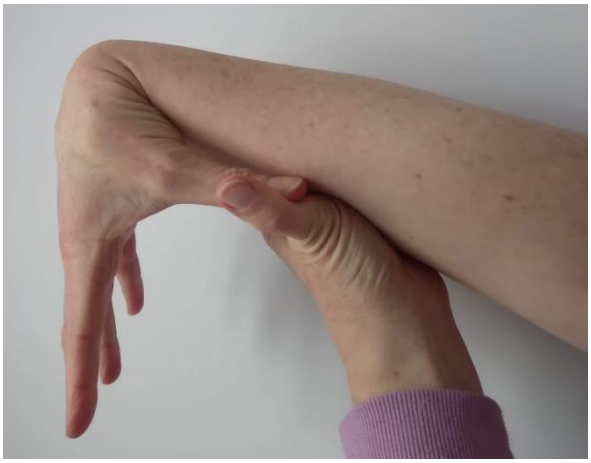


Figure 4.8 Beighton Score Item 2 Passive hyperextension of the elbow. Score is positive if ≥10 degrees (Bilateral Testing)

Figure 4.9 Beighton Score Item 3 Passive hyperextension of the knee. Score is positive if ≥10 degrees (Bilateral Testing)





a **b**

Figure 4.10 Beighton Score Item 4 Passive apposition of the thumb. Score is negative if the whole thumb does not touch the flexor side of the forearm (a) and is positive is the whole thumb touches the flexor side of the forearm (b)

a **b**

Figure 4.11 Beighton Score Item 5 Forward Flexion of the trunk, with knees straight. Score is positive is the hand palms rest easily on the floor (a), or negative if the hand palms cannot rest easily on the floor (b)

4.2.8.4 Muscle endurance

Muscle endurance was measured using the straight leg-lift manoeuvre from the Childhood Myositis Assessment Scale (229, 250). This scale is used widely in paediatric rheumatology clinics. Standardised procedures were followed as detailed in the protocol (Appendix 20). The CMAS has been demonstrated to have excellent validity, interrater and intrarater reliability (229). Normative data are available for healthy children (250).

Scoring: The number of seconds of straight leg-lift duration was recorded in seconds (229). The final score was the maximum time (s) recorded in either leg.

4.2.8.5 Muscle length

Muscle length was assessed as it has been used in previous studies of children and adolescents with symptomatic hypermobility, in combination with other tests, to assess connective tissue laxity (116). Hamstring length was assessed using the Knee Extension Angle (KEA). The popliteal angle was calculated as follows: 180 degrees – KEA. The popliteal angle is often reported in literature and was used in analyses. This test has been shown to be valid and reliable (251). The universal goniometer was used to measure the degree of terminal knee flexion, from terminal knee extension (Figure 4.12) (252). The universal goniometer is cheap, easy to use and commonly used in clinical evaluations of patients (52). Standardised procedures were followed as detailed in the protocol (Appendix 20).

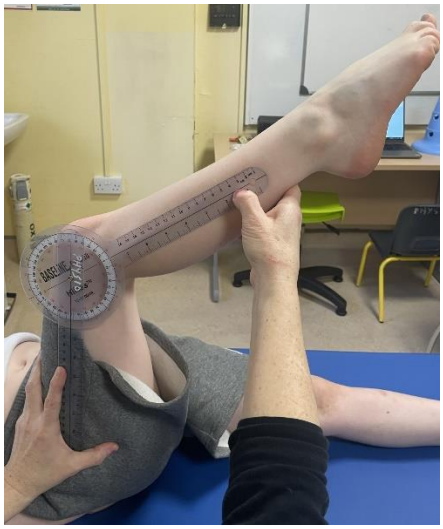


Figure 4.12 Knee Extension Angle Test

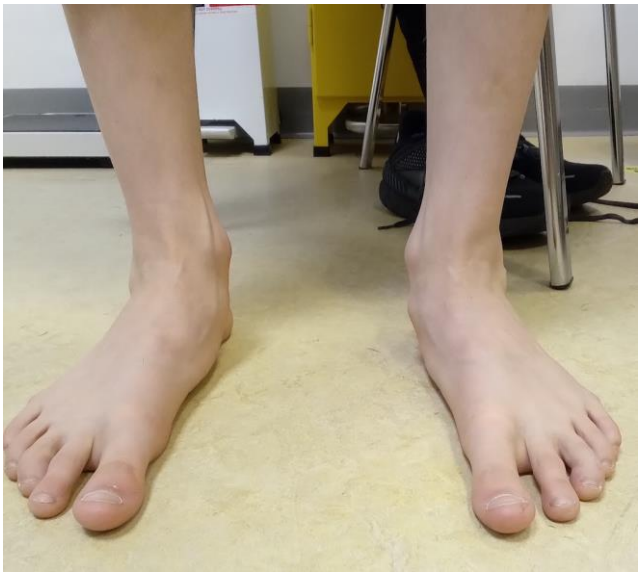
4.2.8.6 Foot posture

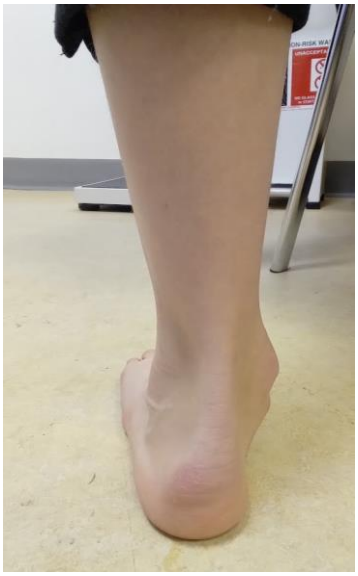
Foot posture was assessed with the Foot Posture Index (FPI-6) which is an observational tool designed to measure the position of the foot. The FPI-6 is conducted using the Reference Sheet (Appendix 27) (230). The FPI-6 is one of the preferred methods of assessing paediatric foot posture as determined by a recent systematic review and has excellent inter-rater reliability (230). The test evaluates the multisegmented nature of foot posture in all three planes and does not require the use of specialised equipment. Each item of the FPI-6 is scored between −2 and +2, with the total six items referring to positions of the forefoot, midfoot and hindfoot, and the three planes of motion: (1) talar head palpation; (2) symmetry of supra and infra lateral malleolar curvature; (3) inversion/eversion of the calcaneus; (4) prominence in the region of the talonavicular joint; (5) height of the medial longitudinal arch; (6) abduction/ adduction of the forefoot (Figure N). Standardised procedures were followed as detailed in the protocol (Appendix 20).

Scoring: The FPI-6 score may range from −12 (highly supinated) to +12 (highly pronated). See Table 4.4 for foot posture index categories.

Table 4.4 Foot Posture Index Categories (182)

Foot Posture Index Reference Values	Foot Posture Category
0 to 5	Normal
+6 to +9	Pronated
10+	Highly Pronated
-1 to -4	Supinated
-5 to -12	Highly Supinated





a **b**

Figure 4.13 Foot Posture Index (FPI-6) positions. Participant stands in their relaxed position with double limb support. Items 1,2,4 and 5 can be observed anteriorly (a), whilst items 3and 6 can be observed posteriorly (b)

4.2.8.7 Strength

Muscle strength is an important aspect of physical fitness and is also considered to be an indicator of overall health (231). There are many tests of muscular strength, but the handgrip strength test has good reliability, and is a useful tool in clinical settings without the need for expensive equipment (253). Grip strength in this study was measured using a Jamar hydraulic dynamometer (Figure 4.14) following the American Society of Hand

Therapists (ASHT) standards, including standards relating to positioning, verbal cueing and reporting the mean of three trials (231). These standardised procedures are detailed in the protocol (Appendix 20). These standards are commonly used in clinical practice, and reference values used in this study, also follow these standards, allowing for age and sex comparison (254). The dynamometer was calibrated as per local clinical guidelines common to each testing setting. The ASHT protocol using the Jamar dynamometer is reliable in children aged 7-13 years with typical development and normative data has been conducted using the ASHT standards in children aged 6 to 19 years old in a well described population in the US (231).

Scoring: The mean of the three measurements for each hand tested was calculated. The scores were normalised for age and sex (231).

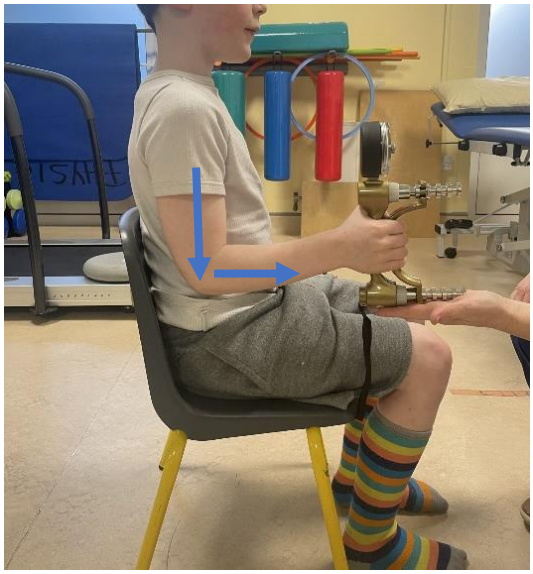


Figure 4.14 Handheld dynamometer standardised positioning (183)

4.2.8.8 Motor skill proficiency

The Bruininks-Oseretsky Test of Motor Proficiency Brief (BOT-2 Brief) was used to screen motor proficiency (232). The BOT-2 is a standardised norm referenced test and assesses motor proficiency from typically developing children and adolescents, to those with mild to moderate motor skill deficits from 4-21 years (232). The BOT-2 has been shown to be

valid and reliable in children aged 4 -21 years old (232). The full version of the BOT-2 takes between 40-60 minutes to complete, with the test divided into eight subtests (255).

The BOT-2 Brief is a version of the BOT-2, which was designed due to the need for a shorter test, and which could be used in a smaller physical space than the full BOT-2 (256). The BOT-2 Brief has 12 items selected from each subscale of the BOT-2 (232, 256). (256). Due to the number of other tests contained in this battery of testing, conducting the full test was not feasible, and the potential for fatigue would mean that this test could not be completed on one testing session. In this study the BOT-2 Brief is not used for a clinical diagnosis of a movement disorder, it was used to provide a single score of overall motor proficiency across eight areas (Figure 4.15). The standardised testing order is sequenced to ensure that items requiring precision and steadiness are not affected by fatigue (Figure 4.15) (256).

1. Fine Motor Precision (sitting)
Filling in a Star
Drawing a Line Through a Path
2. Fine Motor Integration (sitting)
Copying Overlapping Circles
Copying a Diamond
3. Manual Dexterity (sitting)
Stringing Blocks
4. Bilateral Coordination (standing)
Touching Nose with Index Fingers-Eyes Closed
Pivoting Thumbs & Index Fingers
5. Balance (gym)
Walking Forward Heel-to-Toe on a Line
6. Strength (mat)
Push Ups
7. Running Speed & Agility (gym space)
One-Legged Side-hop
8. Upper Limb Coordination (gym space)
Catching a Tossed Ball-1-Hand
Dribbling a Ball-Alternate Hands

Figure 4.15 Bruininks-Oseretsky Test of Motor Proficiency Brief content and order (256)

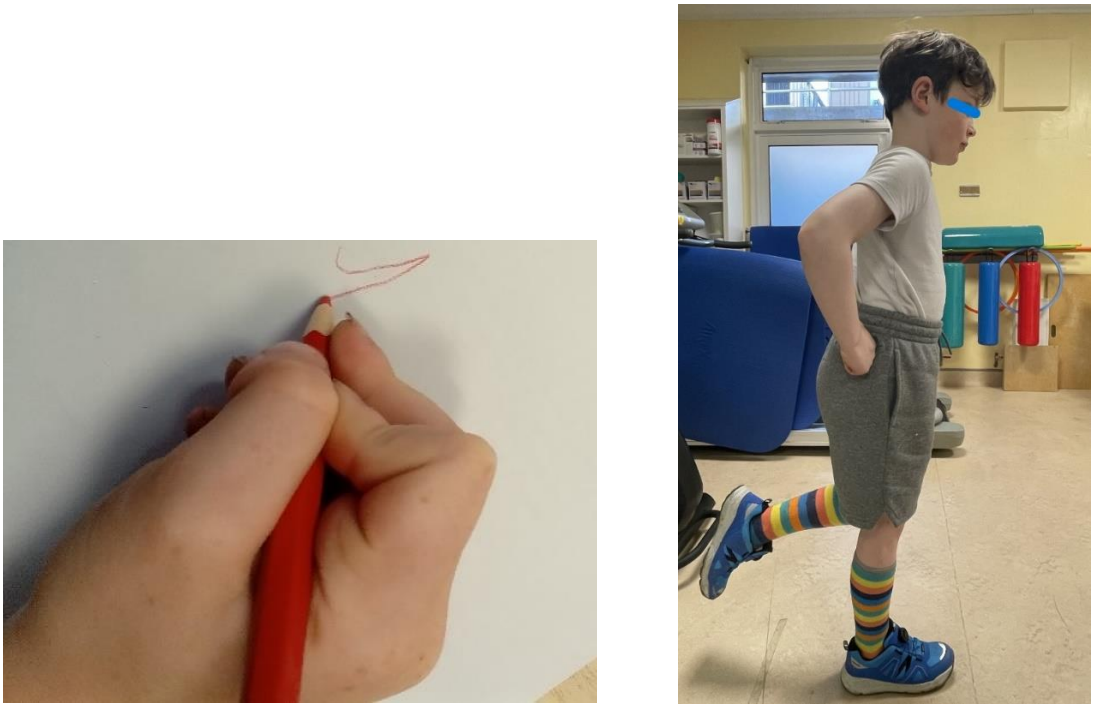
Whilst further studies in more diverse populations are needed, the BOT-2 Brief has been found to be valid and reliable in typically developing children, individuals with developmental coordination disorder, and high functioning autism, between the ages of four and 21 (232, 256-258). The BOT-2 Brief is a standardised test, and therefore careful adherence to the procedures were followed, as per strict instructions using the manual and administration easel (232).

Scoring: Following the completion of each test, the point score was calculated, and the manual conversion table was used to convert the point score to an age and sex normalised standard score and a percentile, and a descriptive term of motor competence (Table 4.5).

Table 4.5 Descriptive categories for the BOT-2 Brief. Correspond to Standard Scores, Percentile Ranks and Standard Deviations. Adapted from (184)

Descriptive Category	**Standard Score Range**	**Percentile Rank Range**	**SD from the Mean**
Well Above Average	70 or greater	98 or greater	2.0 or greater
Above Average	60-69	84-97	1.0 to 2.0
Average	41-59	18-83	-1.0 to 1.0
Below Average	31-40	3-17	-2.0 to -1.0
Well Below Average	30 or less	2 or less	-2.0 or less

BOT-2 Brief Bruininks-Oseretsky Test of Motor Proficiency



a b

Figure 4.16 Bruininks-Oseretsky Test of Motor Proficiency Brief fine motor skill proficiency (a) and gross motor skill proficiency (b) (256)

4.3 Calibration

The Jamar hand dynamometer, weighing scales and height measuring instruments were calibrated before testing began and at 6 monthly intervals.

4.4 Feasibility study

A feasibility study was conducted during the period of January to March 2021. This was also the period of time which coincided with an Irish Government society lockdown policy occurring due to the Covid-19 pandemic. At this time, access to all health settings, patients, parents, other clinicians, and researchers was severely restricted as the Irish Government enforced the most severe level 5 lockdown. Due to these restrictions, the Study II testing protocol was conducted on a convenience sample of three children (n=3) within the same family cohort to reduce any risks to health of children or adults during this unprecedented level 5 lockdown. Three healthy children were included in the

feasibility study within the age categories deemed suitable for inclusion to the study (6-year-old, 10-year-old, and 12-year-old. Outcome measure procedures were already familiar to the Principal Investigator, having previously used these specific outcome measures extensively in clinical practice. Standardised instructions were followed for each test, as per the standardised protocol (Appendix 20). Task familiarisation was not necessary, as strict guidance was followed using the standardised instructions.

4.5 Testing order

Following the feasibility study, the testing order was decided, this order was strictly followed for every test (Figure 4.17). The PedsQL™ 4.0 Generic Scale was completed before the other health questionnaires as per the PedsQL™ administration guidelines, and before the structured interview (259). The questionnaires pertained to specific time periods prior to the testing period and therefore testing was not deemed to influence the results of the questionnaires. The 6MWT was the first objective test to be conducted. This was necessary as the test was carried out according to the American Thoracic Society (ATS) guidelines (227) which specifically deemed a "warm-up" period should not be performed prior to the test (227). The 6MWT was followed by the Y-Balance Test (YBT) which required a suitable warm up (228).

4.6 Testing standardisation and consideration of fatigue

All clinical measurements were conducted following strict standardised protocols. During the YBT, six practice trials were carried out to reduce the learning effect. Fatigue was minimized by alternating stance limbs and following a standardised test order. The stance foot was aligned at the same point each time, to ensure a reproducible position (228). Finally, the BOT2Brief motor skill proficiency test was conducted last (Figure 4.16). This test was the longest (12-15 minutes testing time) and followed a period of testing supine or sitting positions to ensure that the participant was as rested as possible. Additional break periods were not included during the overall testing procedures. The objective

tests included changes in positioning (supine to sitting to standing). These changes of position acted as break periods during the testing, to control for fatigue.

4.7 Randomisation

Three tests which used the same supine testing position (i) the Lower Limb Assessment Scale, ii) Hamstring Length and iii) Muscle Endurance were randomised to minimise order effects. Randomisation was performed using the RAND function in Excel (Microsoft Corporation, Microsoft Excel, 2018). When measuring consecutively between right and left sides (Foot Posture Index, Hamstring length, Muscle Endurance, Lower Limb Assessment Scale); the first side to be measured was always randomly chosen.

The time of day was considered during testing. Due to different Covid-19 policies at three different clinical sites, the time of day was not possible to control.

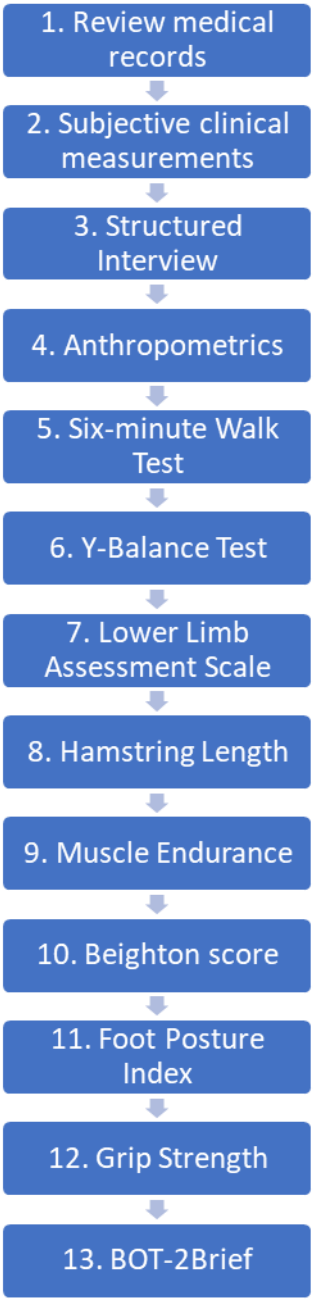


Figure 4.17 Order of Testing for Study II. The Lower Limb Assessment Scale, Hamstring Length and Lower Leg Endurance Test were randomised to minimise order effects

4.8 Study size

This study was an observational, cross sectional study design. To fulfil the aims of the study, all patients presenting to the paediatric rheumatology clinics in CHI who fulfilled the inclusion/exclusion criteria were eligible for inclusion to the study. The number of

participants was dependant on the number of cases presented in the timeframe and was expected to be up to n=300 eligible participants over the time period of 18 months.

4.9 Statistical methods

Statistical analysis took place in the Discipline of Physiotherapy in Trinity College, Dublin and was conducted by the Principal Investigator using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.) Quantitative data were tested for normality using the Shapiro-Wilk test, visually assessing histograms, and box and whisker plots. Continuous variables were reported as mean and standard deviation for parametric data, and median and interquartile range (IQR: Q1, Q3) for non-parametric data. Groups were compared using Independent-samples t tests and one-way analyses of variance for continuous, normal data. Groups were compared using Mann-Whitney U test for skewed data (260). Categorical data were described using frequencies and percentages and groups. Chi-squared or Fisher's exact tests were used to compare categorical data. The strength and direction between continuous variables were examined, using Pearson for continuous variables and Spearman's rank correlation analysis was used for skewed data. Positive values for r were taken to indicate a positive association, whilst negative values were taken to indicate a negative association. Effect sizes were determined using Cohen's d, where values between 0.10 to 0.29 are considered a small effect size, values between 0.30 to 0.49 as moderate and values ≥0.5 considered a strong effect (261, 262). Statistical significance was taken at the level of alpha (α) <0.05 for all measures (two-tailed).

Age and sex adjusted normative data were available for 6-minute walking distance (248), Grip strength (231) and BOT-2 Brief (256). Physical Activity Levels were categorised according to the achievement of cut-off values in the total PAQ scores. PAQ scores of 2.9 for males, and 2.7 for females were identified as cut-off points for UK children and were used in this study (240).

4.9.1 Missing data and outliers

Missing data were reported where present, and was minimal, therefore reducing the impact on statistical analysis (263). Outliers were reviewed to check that errors were not made in data entry, or data collection. Descriptive statistics were conducted to identify the characteristics of the sample, identifying outliers where present as some analyses were more sensitive to outliers than others. In this study, outliers were present in the measures of foot posture and hypermobility but were kept as they were important in the description of the sample.

4.9.2 Statistical analysis

Hierarchal cluster analysis was used in this study to identify if subgroups could be found in the data based on multiple collected objective variables (218). In order to quantify how dissimilar samples are from each other (or nearness), a dissimilarity, or distance measure is used (213). The dissimilarity measure 'squared Euclidean distance' is a widely used measure, intended to use with continuous variables, has a more straightforward interpretation, and was therefore used in this study (218). Euclidean distance is sensitive to the scale of data, and therefore variables were standardised prior to cluster analysis (213). Clusters were combined using Ward's method as it been used in similar research (264), has consistently been shown to demonstrate good recovery of known cluster structure (213) and following comparison with alternative methods (e.g. between-groups linkage), it identified the most clearly defined clinically meaningful clusters within the data in the current study (265). The clinical data in this study contained different types of data, measured on different scales, and therefore, several key steps were taken (218). The first step was to identify which variables, (referred to as features) would be most suitable for use in the cluster analysis. The process used to determine the inclusion or exclusion of variables in the cluster analysis was multifactorial. The set of cluster features used within the cluster analysis were selected based upon: i) reported validity and reliability, ii) consideration of collinearity via pairwise correlations, iii) features which were continuous variables with gaussian-distribution (as this method involves the calculation of cluster means (218), iv) where features were found to be strongly

associated, the cluster model only needed one, as the second would not add any additional information, v) previous studies using similar methodologies (76, 85, 86, 116) and finally, vi) clinical expertise of Principal Investigator, research team and statistical support team. The resulting clusters were then interpreted theoretically and clinically, using the resulting dendrogram, analysis of subgroups and clinical interpretation (266).

The second step of the cluster analysis considered the management of missing data. Complete case analysis (cluster features had no missing entries, or removing samples for which any cluster feature was missing) was deemed appropriate in this data set as the numbers of missing data were extremely small. Missing data were therefore excluded from analyses and are highlighted throughout the text, tables, and figures as appropriate with accompanying reasons. Although there is no agreed consensus regarding the minimal sample size, the larger the number of features used would require a larger sample size (218, 267) (Table 4.6). Using a clustering methodology determined that as large a sample could be collected as possible, to fulfil the aims and objectives of the study. Dolnicar et al., recommended n=70 per cluster feature, but there is no universal rule of thumb (267). Previous exploratory studies, using similar statistical methods to the current study, have used sample sizes n=105 (76) and n=89 (85). Liaison and support from a university-based Centre for Support and Training in Analysis and Research (CSTAR) was sought during the hierarchal cluster analysis stage. Following liaison with CSTAR to determine the sample size required for cluster analysis, the following sample sizes per cluster feature were suggested (Table 4.6 – Appendix 30).

Table 4.6 Number of variables or features and range of sample sizes (268)

Number of Features	**N**	
	Minimum	**Preferred**
5	32	160
7	128	640
10	1024	5120

The selected features were then considered if they required scaling, or transforming, based on the type of data, and the scale used. Continuous data were all measured on different scales. Due to this, they were standardised to have 0 mean and unit variance (z-score).

Once the final cluster solution was determined, the mean and SD of test scores were reported for each subgroup and analysis of variance (ANOVA) was performed to test for significant differences in individual test scores between the groups. The differences between means of other patient characteristics were also explored using ANOVA. Chi-squared or Fisher's exact tests were used to compare categorical data between final cluster groups.

4.10 Data management

4.10.1 Data storage and access

Participant data were collected on one occasion. All study data were pseudonymised using a study identification (study ID) number. Hard copy collected data were stored in a locked filing cabinet, in a locked office in the tertiary children's hospital. A hard copy of the study ID was recorded on a patient master identification list and kept separately, in a different locked office, in the tertiary children's hospital. Data were stored on an encrypted password protected electronic database on a laptop, this was only accessed by the Principal Investigator.

Data Protection Impact Assessments containing full details of data management including data type, access, and storage, were conducted for both academic (Trinity College Dublin), and clinical (Children's Health Ireland) sites (Appendices 10 & 11). Data will be stored for a total of seven years to allow for study analysis and potential publication of findings. It will then be destroyed in line with academic and clinical institution procedures.

4.10.2 Participant feedback reports

Each study participant received a brief report on completion of the testing phase of Study II. If any medical issues arose during the assessment, email correspondence was sent to the referring consultant or clinical specialist physiotherapist, and the parent and CPY participant was advised to follow up with the referring practitioner.

4.11 Results

4.11.1 Recruitment

Overall, a total of eighty participants (54 females and 26 males), mean age 11.6 (3.0) years, range 6.0 -16.9, and mostly female (67.5%, n=54/80) along with eighty parent/guardians of the participants were recruited and enrolled in the study. There were no participants who declined to take part in the study. There were no dropouts during the testing phase, as all participants attended for testing and attempted all the testing procedures. Recruitment began in June 2021. Data collection took place over an 18-month time period between July 2021 and January 2023. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria (Appendix 6) were followed (25).

4.11.2 Feasibility study

Three healthy children were included in the feasibility study within the age categories deemed suitable for inclusion to the study (6-year-old, 10-year-old, and 12-year-old). A number of trials took place to establish the timing of each measure, order and useability of testing protocol. Testing took place indoors, with the exception of the 6-minute walking test which was conducted on an outdoor, 30m track. This feasibility study found that the testing order was very important, and of particular relevance to the youngest child, who required more periods of rest, and also struggled to keep attention during longer tests, such as the BOT-2 Brief.

4.11.3 Participant demographics

The demographics of the participants are presented in Table 4.7. The median (IQR: Q1, Q3) BMI centile was 64.5 (25, 87.3) with 17.3% (n=4) of children (6-9 years) and 31.5% (n=18) of adolescents (10-16 years) were overweight or obese. Ethnicity was reported according to the Central Statistics Office census 2021, participants were mostly Caucasian; white Irish 92.5% (n=74/80) or white 'other' 2.5% (n=2/80) and Asian participants accounted for 5.0% (n=4/80). More participants were classified with generalised hypermobility according to the Beighton score (77%, n=62/80), than with the Lower Limb Assessment Scale (60%, n=48/80), whereas combining the two, 88% (n=70) of participants were identified as having generalised hypermobility. The median (IQR: Q1, Q3) length of time to diagnosis or recognition of symptomatic hypermobility was twenty-four months (12, 48). Recalling an event prior to the onset of symptoms was reported in 30.0% (n=24/80) of participants, listing an injury (13.8%, n =11/80) or a virus (13.8%, n =11) prior to the onset of symptoms. Only 32.5% (n=26/80) of participants could be defined as physically active (cut-off score (>2.9 PAQ male; >2.7 PAQ female) (240). Above and well above average motor skills were recorded in only 7.6% (n=6/79) of participants, and 44% (n=35/79) of the sample had below or well below average motor skills.

Table 4.7 Demographics (n=80)

Characteristic	n (%)
Age	
Child 6-9 years	23 (28.8)
Adolescent 10-16 years	57 (71.3)
Biological sex	
Female	54 (67.5)
Male	26 (32.5)
BMI (kg/m^2) centile category [a]	
Underweight	3 (3.8)
Healthy weight	55 (68.8)
Overweight	13 (16.3)
Obese	9 (11.3)
Generalised joint hypermobility	
≥6 Beighton score	62 (77.5)
≥7 LLAS	48 (60.0)
≥6 Beighton score OR ≥7 LLAS	70 (87.5)

[a]BMI centile: centiles for BMI and height are calculated for age from gender-specific reference values; LLAS Lower Limb Assessment Scale. Data are presented as frequency and percentage unless otherwise specified.

4.11.4 Medical chart review and structured interview

4.11.4.1 Additional diagnoses

Additional diagnoses were self-reported by the parent or child/adolescent participant during structured interview (Appendix 17) by asking 'Do you have any additional diagnoses?' and also verified in the medical chart (Table 4.8). The presence of additional diagnoses was extremely common, with 90.0% (n=72) of participants reporting the presence of at least one other condition. Neurodevelopmental diagnoses were the most frequent. Developmental co-ordination disorder was reported in nearly one quarter of all participants (23.8%, n=19/80), a diagnosis of Autistic Spectrum Disorder or Attention Deficit Disorder was reported in 16.3% (n=13/80) of participants and 20.0%, (n=16/80) reported more than one neurodevelopmental diagnosis.

Table 4.8 Additional diagnoses (n=80)

Additional diagnosis (self-reported and verified in the medical chart)	n (%)
Neurodevelopmental	39 (48.8)
Allergy	20 (25.0)
Gastrointestinal	16 (20.0)
Anxiety	10 (12.5)
Primary Dysautonomia	10 (12.5)
Scoliosis	9 (11.3)
Mild bleeding disorder	8 (10.0)
Headache	4 (5.0)
Functional bladder disorder	2 (2.5)

4.11.4.2 Medication

Medication usage was as follows: NSAIDS/analgesia (27.5%, n=22/80), laxatives (21.3%, n=17/80) reflux (16.3%, n=13/80), orthostatic intolerance (11.3%, n=9/80), asthma (8.8%, n=7/80), allergy (8.8%, n=7/80), melatonin (7.5%, n=6/80), antianxiety/depression (2.5%, n=2/80) and urinary (1.3%, n=1/80). High medication usage (defined as greater than 3 types of medication) was reported in 13.8%, n=11 participants.

4.11.4.3 Multi-systemic complaints

Multi-systemic complaints assessed during structured interview and reviewed in the medical chart are presented below in Table 4.9. Multi-systemic complaints were assessed using a number of screening questions, which had been informed by Study I. Complaints were based on subjective reports.

Chronic pain in at least one joint was present in 100% (n=80) of participants. Chronic pain in 3 locations or more was reported in 62.5% (n=50/80) of participants. The lower limb was more commonly painful (95.0%) compared to the upper limb (62.5%) and spine (32.5%). The most frequently reported locations were knee (72.5%, n=58/80), ankle (55.0%, n=44/80) and fingers (37.5%, n=30/80). Joint instability (perceived dislocation or

subluxation) was reported by 26.3% (n=21/80) of participants. Joint instability was reported in greater frequency in adolescents (29.8%, n=17/57), compared to children (17.4%, n=4/23). Patellar instability was most commonly reported (10.0%, n=8/80), followed by the shoulder (7.5%, n=6/80) and small joints of the fingers or thumbs (6.3%, n=5/80). Five (6.3%) instability episodes were severe enough to warrant hospital attendance and seven (8.8%) instability episodes required further investigation.

Complaints of Orthostatic Intolerance (OI) were reported by 40.0% (n=32/80) of overall participants. A greater frequency of OI was reported in adolescents (49.1%, n=28/57) compared to children (17.4%, n = 4/23). Of those reporting complaints, 11.3% (n=9/80) were on medication for symptoms.

Gastrointestinal complaints were reported in greater frequency than Gastrointestinal diagnoses. Gastrointestinal complaints included constipation (30.0%, n=24/80), diarrhoea (13.8%, n = 11/80) and reflux (12.5%, n=10/80).

Skin features most commonly reported were soft or doughy skin (8.8%, n=7/80), the presence of atrophic scars (8.8%, n=7/80), mild skin extensibility 5.0% (n=4/80), and the presence of unexplained striae in 3.8% (n=3).

Urinary incontinence (stress or urge) was reported in 20.0% (n=16/80) of participants during the structured interview, more commonly reported in children (30.4%, n=7/23) than adolescents (15.8%, n=9/57).

Multi-systemic complaints were expressed as a percentage of the included population (n=80), with those reported by 10% or greater reported in Table 4.9.

Table 4.9 Multisystem complaints according to clinical domains (n=80) assessed during structured interview and reviewed in the medical chart

Clinical domain	Type of symptom	n (%)
Musculoskeletal	Chronic joint pain	80 (100.0)
	Joint Instability	21 (26.3)
Cardiovascular	Orthostatic Intolerance	32 (40.0)
Gastrointestinal	Constipation	24 (30.0)
	Diarrhoea	11 (13.8)
	Reflux	10 (12.5)
Cutaneous	Soft/doughy	7 (8.8)
	Atrophic scars	7 (8.8)
	Mild skin extensibility	4 (5.0)
	Unexplained striae	3 (3.8)
Ocular	Short sighted, long sighted, other (blue sclera, stigmatism, tracking issues)	24 (30.0)
Headaches	Headache	22 (27.5)
Urogenital	Incontinence (urgency, stress)	16 (20.0)

4.11.4.4 School Engagement

School attendance in the last year, was reported as ≥80% engagement in 91.3% (n=73/80) of participants. All but one participant attended in-school lessons with one participant attending school at home.

4.11.5 Clinical measurements

4.11.5.1 Self-reported questionnaires

There were no missing values from child or parent respondents in any of the four questionnaires. One child (8-year-old) used a younger child (5-7 years old) questionnaire due to issues related to reading and comprehending the age specific (8-12 years old)

questionnaire. This was permitted within the protocol, and therefore the results were included.

Quality of Life

Eighty parent/guardians completed the parent proxy-report PedsQL questionnaire, and 80 participants completed the self-report PedsQL questionnaire. Table 4.10 presents Peds QL child self-report, parent proxy-report total and subscale scores, in comparison to scores from a normative population (223). Mean PedsQL scores were significantly lower than the normative population for both self-reported and parent-proxy reported in each subscale (Table 4.10). Mean Peds QL self-report total scores were significantly lower for females than males (p = .01). Parents ratings of perceived quality of life were a good proxy for their children (r = .63, p = <.001) (Appendix 28).

Table 4.10 PedsQL™ 4.0 Generic Core Scale scores and comparison with normative population

PedsQL™ 4.0 Generic Core Scale (0-100)	**Study population**	**Normative population**	***p*-value**	**Effect size** [a]
	Mean (±SD)	**Mean (±SD)**		
Self-report n = 80				
Total score	60.0 (18.2)	83.0 (14.8)	<.001*	-1.3
Physical health	55.3 (21.0)	82.4 (15.5)	<.001*	-1.4
Psychosocial health	64.1 (19.0)	82.4 (17.3)	<.001*	-0.9
Parent proxy-report n = 80				
Total score	55.1 (16.5)	87.6 (12.3)	<.001*	-2.0
Psychosocial health	59.4 (18.2)	86.6 (12.8)	<.001*	-1.5
Physical health	50.2 (17.7)	89.3 (16.4)	<.001*	-2.2

PedsQL™ 4.0 Generic Core Scale 0-100 where higher number indicates better quality of life. [a] Negative effect size indicate lower quality of life compared with normative population (223). * significance level p < 0.05. Data are presented as mean ± SD unless otherwise specified.

Mean Peds QL self-report and parent-proxy total scores were plotted in relation to mean scores from healthy children (223), children with newly diagnosed Juvenile Idiopathic Arthritis (269), survivors of childhood central nervous system (CNS) tumours (235) and paediatric cardiac patients (234) (Figure 4.18).

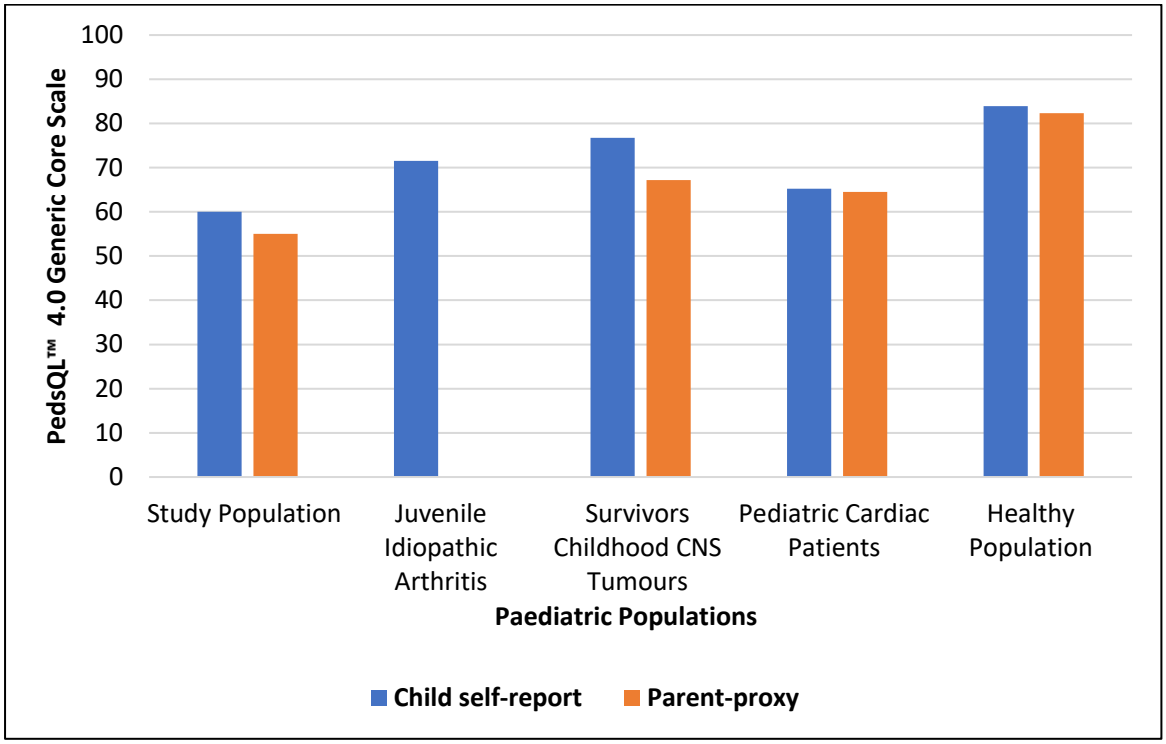


Figure 4.18 Quality of life self-report and parent-proxy total scores. Measured by PedsQL™ 4.0 Generic Core Scale 0-100 where higher number indicates better quality of life. Parent-proxy scores not available for Juvenile Idiopathic Arthritis sample (269)

Pain

Eighty parent/guardians completed the parent proxy-report PedsQL™ Paediatric Pain Questionnaire, and 80 participants completed the self-report PedsQL™ Paediatric Pain Questionnaire. Self-reported child and parent-reported present pain and pain in the past-7 days are summarised in Table 4.11. Pain severity in the past 7-days was greater, than present pain ('moderate' severity compared to 'mild' severity), in both self-report and parent proxy-report. Males did not have significantly lower mean pain in the past-7 days (M = 4.4, SD = 2.7) compared to females (M = 5.8, SD = 2.8; t (78) = -2.0, p = 0.05). Parents

ratings of their child's worst pain over the past 7-days, were a good proxy for their child (r= 0.604, *p* = < .001) (Appendix 28).

Table 4.11 Pain severity measured by PedsQL™ Paediatric Pain Questionnaire for present pain and pain over the past 7-days

PedsQL Pain VAS (0-10)	**Child self-report (n=80)**		**Parent proxy report (n=80)**	
VAS	**Present pain VAS Mean (±SD)**	**Pain in past 7-days VAS Mean (±SD)**	**Present Pain VAS Mean (±SD)**	**Pain in the past 7-days VAS Mean (±SD)**
Total	2.6 (2.8)	5.3 (2.8)	3.4 (2.6)	4.7 (3.2)
Male	2.0 (2.4)	4.4 (2.7)	2.8 (2.2)	3.8 (3.2)
Female	2.9 (2.9)	5.7 (2.8)	3.7 (2.8)	5.2 (3.0)

VAS visual analogue scale. VAS scores 0-10 where higher numbers indicates more severe pain. Data are presented as mean ±SD

Fatigue

Eighty parent/guardians completed the parent proxy-report PedsQL™ Multidimensional Fatigue Scale and 80 participants completed the self-report PedsQL™ Multidimensional Fatigue Scale. Total scores and subscale (general, sleep/rest and mental fatigue) scores are presented in Table 4.12, with comparison to a healthy paediatric sample (270). Mean fatigue scores were significantly lower than normative population scores in every subscale for both self-reported and parent proxy reported fatigue (*p* <.001).

Table 4.12 PedsQL™ Multidimensional Fatigue Scale and comparison with normative population

PedsQL™ Multidimensional Fatigue Scale (0-100)	Study population	Normative population	*p*-value	Effect size[a]
	Mean (±SD)	Mean (±SD)		
Self-report n = 80				
Total score	57.1 (21.9)	80.5 (13.3)	<.001*	-1.1
General fatigue	58.2 (24.1)	85.3 (15.0)	<.001*	-1.1
Sleep/rest fatigue	59.9 (20.2)	75.0 (18.8)	<.001*	-0.7
Mental fatigue	54.6 (28.4)	81.1 (17.4)	<.001*	-0.9
Parent proxy-report n = 80				
Total score	53.0 (18.6)	89.6 (11.4)	<.001*	-2.0
General Fatigue	47.9 (20.8)	89.3 (13.3)	<.001*	-1.5
Sleep/rest fatigue	59.2 (19.5)	88.9 (14.)	<.001*	-1.5
Mental fatigue	51.9 (26.3)	90.7 (15.2)	<.001*	-2.0

Data are presented as mean ± SD unless otherwise specified. PedsQL™ Multidimensional Fatigue Scale score 0-100 where higher number indicates less fatigue. [a] Negative effect size indicate lower fatigue compared with normative population (270). * significance level $p \leq 0.05$

Mean fatigue self-report scores were significantly lower for females than males (p = 0.01). Mean fatigue self-report scores were significantly lower in adolescents than children (p = 0.01). Comparing the absolute mean scores across the subscales, study participants reported more mental fatigue than general fatigue, and sleep/rest. Parent ratings of total fatigue were a reasonable proxy for their children (r = .49, p = <.001) (Appendix 28).

Physical Activity Levels

Descriptive statistics including the mean and SDs of the total Physical Activity Questionnaire (PAQ) scores by biological sex, child (6-9 years) and adolescent (10-16 years) are summarised in Table 4.13. Males (M=2.7, SD = 0.8) were significantly more active than females (M=2.2, SD 0.7; t (78) = 2.8, p = 0.01). Neither group mean reached

the cut-off levels (male PAQ 2.9 and female PAQ 2.7) required to achieve the category of 'sufficiently active' (240) (Table 4.13).

Item one of the PAQ asked participants to tick which sports or activities they had participated in the last week. Of the 76 participants who reported taking part in at least one sport in the past week, 63.2% (n=48/76) marked individual sports such as walking (n=24/76), swimming (n=24/76), or dance (n=8/76) and gymnastics (n=8/76). Team sports were reported in 36.8% (n=28/76) of participants, including Gaelic football (n=16/76), soccer (n=8/76), basketball (n=8/76) and hurling/camogie (n=6/76).

Table 4.13 Physical Activity measured by Physical Activity Questionnaire (PAQ)

	PAQ score (1-5) Mean (±SD)
Total (n=80)	2.4 (0.7)
Male	2.7 (0.8)
Female	2.2 (0.6)
Child 6-9 years	2.6 (0.6)
Adolescent 10-16 years	2.3 (0.7)

PAQ Physical Activity Questionnaire. Data range from 1-5 where higher scores indicates greater physical activity levels. Data are presented as mean ± SD

Descriptive statistics for the four questionnaire measures are summarised in Table 4.14. Overall females had worse quality of life (p = 0.01), levels of general and cognitive fatigue (p = 0.02 and p = 0.02) and physical activity scores than males (p = 0.01). There was no significant difference between males and females with respect to age, or BMI.

Table 4.14 Descriptive statistics of self-reported questionnaires

Outcomes	Total (n = 80)	Male (n=26)			Female (n=54)			*p*-value	MD	95% CI
		Mean (±SD)	Min	Max	Mean (±SD)	Min	Max			
Age (years)	11.6 (3.0)	11.3 (2.7)	6.1	16.5	11.7 (3.2)	6.0	16.9	0.56	-0.4	-1.8 to 1.0
Gender n (%)		26 (32.5)			54 (67.5)					
BMI centile	59.4 (29.3)	58.6 (30.6)	4	99	59.7 (28.9)	1	97	0.80	-1.1	-15.1 to 12.8
Total QOL (0-100) [a]	60.0 (18.2)	67.2 (19.7)	19	99	56.6 (16.6)	21	94	0.01*	10.6	2.2 to 19
Physical domain	55.3 (21.0)	63.9 (24.5)	13	100	51.2 (18.5)	13	90.6	0.01*	12.6	3.1 to 22.2
Psychosocial domain	64.1 (19.0)	69.8 (19.3)	25	100	61.3 (18.4)	25	96.7	0.05	8.6	-0.2 to 17.4
Pain severity VAS (0-10) [b]	5.3 (2.8)	4.4 (2.7)	0	10	5.8 (2.8)	0	10	0.05	-1.3	-2.6 to 0.01
Total fatigue (0-100) [a]	57.1 (21.9)	66.1 (22.4)	11.1	98.7	52.9 (20.5)	15.3	91.7	0.01*	13.2	3.2 to 23.3
General fatigue	58.2 (24.1)	66.7 (23.7)	4.2	100	54.2 (23.5)	8.4	100	0.02*	12.5	1.3 to 23.7
Sleep/Rest Fatigue	59.9 (20.2)	66.0 (21.0)	20.8	95.9	57 (19.3)	20.9	95.9	0.06	9.0	-0.3 to 18.4
Cognitive Fatigue	54.6 (28.4)	66.6 (28.2)	0	100	49.2 (27.2)	0	100	0.02*	16.3	3.2 to 29.3
Physical Activity (1-5) [c]	2.4 (0.7)	2.7 (0.8)	1.57	4.22	2.2 (0.65)	1.22	3.91	0.01*	0.5	0.13 to 0.79

Data are presented as mean ± SD unless otherwise specified. [a] higher score indicates higher QOL and lower fatigue levels. [b] Higher score indicates worse pain levels in the past 7-days. [c] A score of 1 indicates low physical activity, whereas a score of 5 indicates high physical activity. QOL Quality of Life; VAS Visual analogue scale; All groups are compared using the Independent Samples T Test unless otherwise specified. * significance level $p < 0.05$ (two-tailed)

4.11.6 Objective tests

Descriptive statistics for all nine objective tests are summarised in Table 4.15. Among the 80 participants, n=1 did not complete the BOT-2 Brief and n=7 did not complete the YBT. The most common reason for not completing either test was a difficultly with the motor skill required to complete the task, or keeping attention. Mean and SD are reported for each objective test, unless otherwise specified. Median LLAS and Beighton score achieved cut-offs for generalised hypermobility (≥7/12 LLAS and ≥6/9 BS) whilst outliers were identifed with low scores recorded in both. The mean foot posture index was 7.0 (2.7) categorised as a pronated foot posture (230). Median (IQR) muscle endurance scores were 52 seconds (31, 120) out of a maximum 120 seconds. Females had signficantly more functional impairment (p = 0.02), longer hamstring length (p = <.001*) and had a higher Beighton score (p = 0.03) than males. Dynamic Balance, Lower Limb Assessment Scale, Muscle Endurance, Strength and Motor Skill Proficiency standard score did not differ between biological sex. In the following sections, results from each objective test will be reported in greater detail.

Table 4.15 Descriptive statistics of objective tests

Outcomes	n	Total	Male (n=26)			Female (n=54)			*p*-value	MD	95% CI
		Mean (±SD)	Mean (±SD)	Min	Max	Mean (±SD)	Min	Max			
Functional Capacity 6MWD (m)	80	518.6 (91.0)	551.4 (86.2)	420	758	502.8 (86.2)	210	687	0.02*	48.5	6.4 to 90.7
Dynamic Balance (cm) YBT [a ǂ]	73	100.3 (13.0)	100.0 (10.9)	82.4	127.8	100.4 (13.9)	69.8	144.0	0.89	-0.4	-6.9 to 6.1
Lower Limb Assessment Scale (0—12) (median IQR) ¥	80	7.0 (5.0, 9.0)	7.0 (4.6, 9.0)	1	11	7.5 (4.8, 9.0)	0	11	0.87 U 718.5 Mean Ranks 39.9 vs 40.8		
Beighton score (0-9) (median IQR) ¥	80	6.0 (6.0, 7.0)	6.0 (4.0, 6.0)	1	8	6.0 (6.0, 8.0)	0	9	0.03* U 907.5 Mean Ranks 32.6 vs 44.3		
Foot Posture Index (-12 to +12) [b]	80	7.0 (2.7)	7.8 (2.5)	3.5	12	6.6 (2.7)	-1	11	0.05	1.3	0.02 to 2.5
Muscle endurance (sec) (median IQR: Q1, Q3) ¥	80	52 (31, 120)	66.5 (36.5, 120.0)	15	120	47 (30, 120)	12	120	0.20 U 579.5 Mean Ranks 45.2 vs 38.2		
Muscle Length (popliteal angle in degrees)	80	145.8 (13.9)	137.9 (9.8)	120	160	149.7 (14.0)	125	180	<.001*	-11	-17.9 to 5.7

Strength (kg)	80	10.4 (6.3)	11.0 (7.1)	2	30	10.1 (6.0)	0	25	0.69	0.6	-2.5 to 3.8
Motor skill standard score [c]‡	79	42.3 (10.2)	43.4 (10.4)	28	69	41.8 (10.1)	20	71	0.49	1.7	-3.19 to 6.6

Data are presented as mean ± SD unless otherwise specified. [a] Normalised to leg length. ‡ total sample n=73 (n=7 did not complete the YBT); [b] Foot Posture Index 0 to +5 Normal, +6 to +9 Pronated, 10+ Highly Pronated, -1 to -4 Supinated, -5 to -12 Highly Supinated; [c] Age and sex adjusted centile, ‡ total sample n=79 (n=1 did not complete); 6MWD 6-minute walk distance; YBT Y-Balance Test; Groups are compared using the Independent Samples T Test unless otherwise specified. ¥ Lower Limb Assessment Scale, Beighton Score and Muscle endurance groups compared using the Mann Whitney U Test. *significance levels p <0.05

4.11.6.1 Functional impairment

The six-minute walk test (6MWT) was completed by all participants (n=80). One participant required the use of a mobility aid to complete the assessment. Participants achieved a mean distance of 518.5m (91.0m), (Range 210 – 758m) on the 6MWT. There was a significant difference between the six-minute walk distance (6MWD) achieved by participants and sex and age adjusted predicted 6MWD (*p* <.001, CI [-129.4, - -86.5), with participants achieving a significantly reduced overall distance in 6MWD (Table 4.16). A significantly large negative effect size was found (-1.6) when measuring the difference in the observed 6MWD of participants and the sex and age adjusted predicted 6MWD (mean difference = 107.96, 95% CI [86, 129.4]).

Table 4.16 Six-minute walk distance in metres

	Observed 6MWD Mean (±SD)	**Predicted 6MWD Mean (±SD)**	***p*-value**
Total population (n = 80)	518.5 (91.0)	626.51 (32.4)	<.001*

Data are presented as mean ± SD. 6MWD as measured by the 6MWT was conducted according to the American Thoracic Society (ATS) guidelines (227). 6MWD Six-minute walk distance; 6MWT Six-minute walk test. *significance levels p <0.05

The distance decreased into later adolescence, in particular in females (Figure 4.19). Children and adolescents completed the self-reported Borg Perceived Exertion Scale (227) following the 6MWT and 38% (n=30) reported their perceived exertion as ‘hard’ or greater.

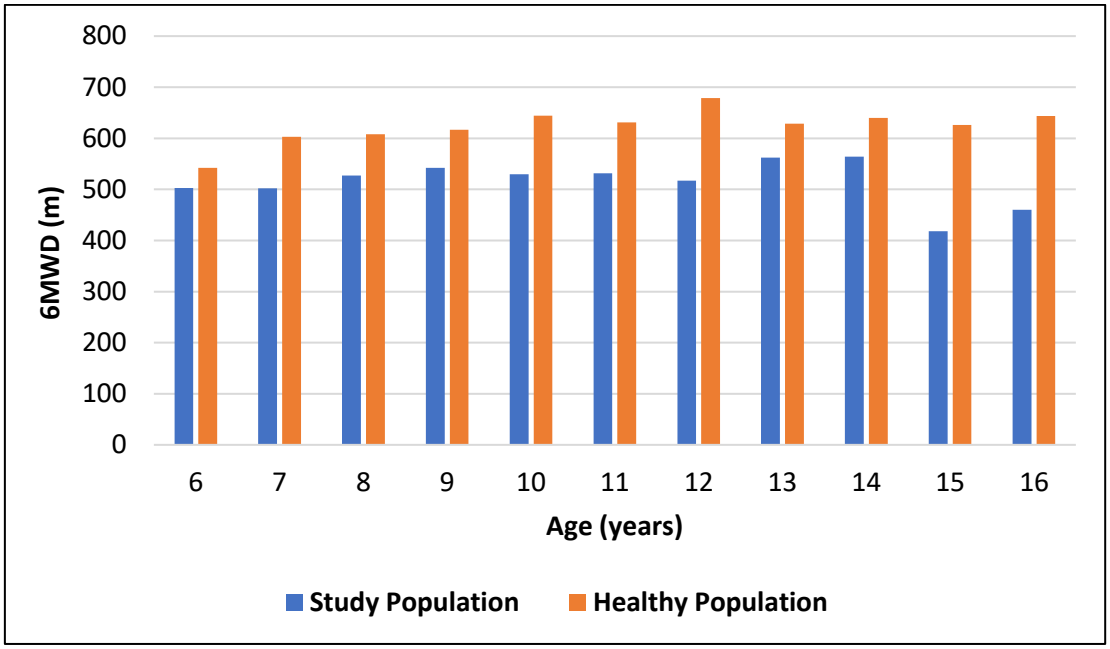


Figure 4.19 Six Minute Walk Distance (m) in participants and a healthy age and sex matched sample

4.11.6.2 Dynamic balance

The Y-balance test (YBT) was fully completed by n= 73 participants. Three participants were unable to complete any part of the YBT. Four other participants were unable to complete parts of the YBT. The Posterolateral reach direction was the most common direction whereby participants were unable to complete the test. Participants who did not complete the test could not maintain a unilateral stance on the platform or had difficulties keeping attention during the test. The seven participants who did not complete the YBT were found to be significantly younger (M = 8.9, SD = 2.3) than the participants who completed the YBT (M = 11.9 (3.0), *p* =0.01). Participants who did not complete the YBT also had worse motor skill proficiency (M = 36.2, SD = 5.8) in comparison to the participants who completed the YBT (M = 42.8, SD = 10.3, p = 0.38). Participants were not found to have significantly more fatigue, pain, worse quality of life, or any other differences in clinical measures. The mean score for the normalised YBT composite reach distances and reach distances in all three directions (mean of anterior, posteromedial and posterolateral) are presented in Table 4.17.

Table 4.17 Normalised Y-balance test composite reach distance and reach distance in each direction (anterior, posteromedial, and posterolateral)

		Total	Male		Female	
Y-balance test reach distances (cm)	**n**	**Mean (±SD)**	**Child Mean (±SD)**	**Adolescent Mean (±SD)**	**Child Mean (±SD)**	**Adolescent Mean (±SD)**
YBT Composite	73	100.3 (13.0)	95.7 (9.0)	101.5 (11.3)	102.9 (16.1)	99.6 (13.2)
YBT Anterior	77	76.5 (9.3)	77.6 (10.4)	75.0 (9.0)	76.8 (9.3)	76.9 (9.6)
YBT Posteromedial	77	113.0 (16.1)	111.1 (10.5)	108.1 (14.0)	116.8 (14.0)	114.3 (18.3)
YBT Posterolateral	75	111.7 (15.7)	113.9 (9.7)	106.4 (14.1)	114.6 (14.0)	112.7 (17.5)

Data are presented as mean ± SD. YBT Y-Balance Test

There was no difference in mean composite YBT scores in males (composite M=100.0, SD=10.9) compared to females (M=100.4, SD = 13.9; t (71) = -1.27, *p* = 0.89). There was no difference in mean composite YBT scores in children aged 6-9 years (composite M = 100.7, SD 14.4) and adolescents aged 10-16 years (composite M = 100.2, SD 12.6; t (71) = 0.14, *p* = 0.89).

4.11.6.3 Generalised hypermobility and muscle length

Generalised hypermobility was screened using the Beighton score (BS) and the Lower Limb Assessment Scale (LLAS). As expected in this cohort, the BS and LLAS were not normally distributed. Higher scores in the Beighton score were associated with higher scores in the Lower Limb Assessment (rho = 0.38, p =.001). Mean muscle length (popliteal angle) was 145.8 (13.9) degrees. Female participants (M= 149.7, SD = 14) had significantly longer hamstring length than male participants (M=137.8, SD 9.8; t (78) = -

3.9, $p < .001$) (Table 4.15). The magnitude of the difference in the means was large (mean difference =-11.8, 95% CI [-17.9, -5.7]). Longer hamstring length was associated with higher Beighton scores (r = .34, $p = <0.002$).

4.11.6.4 Muscle endurance

Muscle endurance as measured by the straight leg-lift manoeuvre from the Childhood Myositis Assessment Scale was completed by all participants (n=80). In comparison to 96-100% of a sample of healthy children aged ≥ 6 years who demonstrated that they could maintain the maximum straight leg-lift time of 120 seconds or greater (≥2 minutes), only 31.3% (n=25/80) of participants achieved the maximum duration for a straight leg-lift of 120 seconds (Figure 4.20). The median (IQR: Q1, Q3) straight leg-lift was 52 seconds (30 - 120).

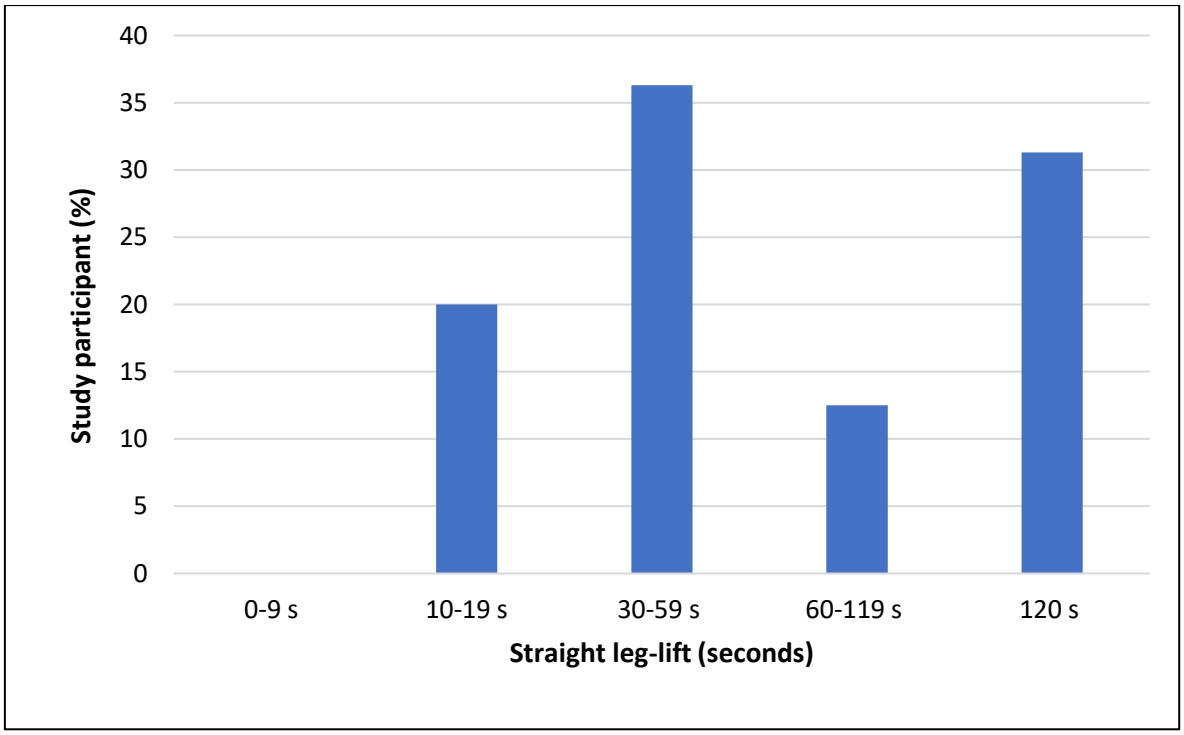


Figure 4.20 Muscle endurance measured by the timed straight leg-lift (seconds)

4.11.6.5 Foot posture

The Foot Posture Index was completed by all participants (n=80). The most common foot posture of childhood is a normal (0 to +5 FPI) foot posture, followed by a pronated foot posture (+6 to +9 FPI) (271). In this study, the most common foot posture was a pronated foot posture (60%, n = 48/80) and 14% (n=11/80) of participants had a highly pronated foot posture (+10 to +12 FPI) (Figure 4.20). The mean Foot Posture Index (FPI) was +6.98 (2.68).

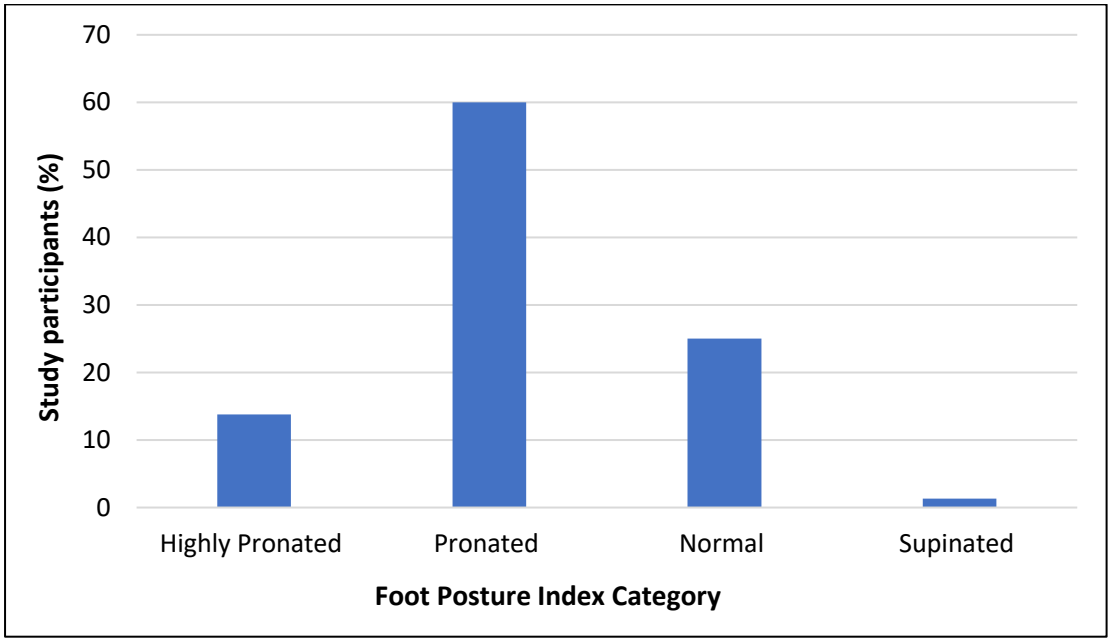


Figure 4.21 Foot Posture Index categories. FPI categories: Highly Pronated +9 to +12 FPI, Pronated +6 to +9 FPI, Normal 0 to +5 FPI and Supinated -1 to -4 FPI (230). FPI Foot Posture Index.

4.11.6.6 Strength

Grip strength testing was completed by all participants (n=80). Descriptive data including mean and standard deviations for average grip strength in kilograms are summarised in Table 4.20. Figure 4.22 compares the study population with an age and sex matched healthy sample (231). Mean grip strength in the study population was significantly lower than the age and sex matched healthy population (mean difference -10.0, p <.001).

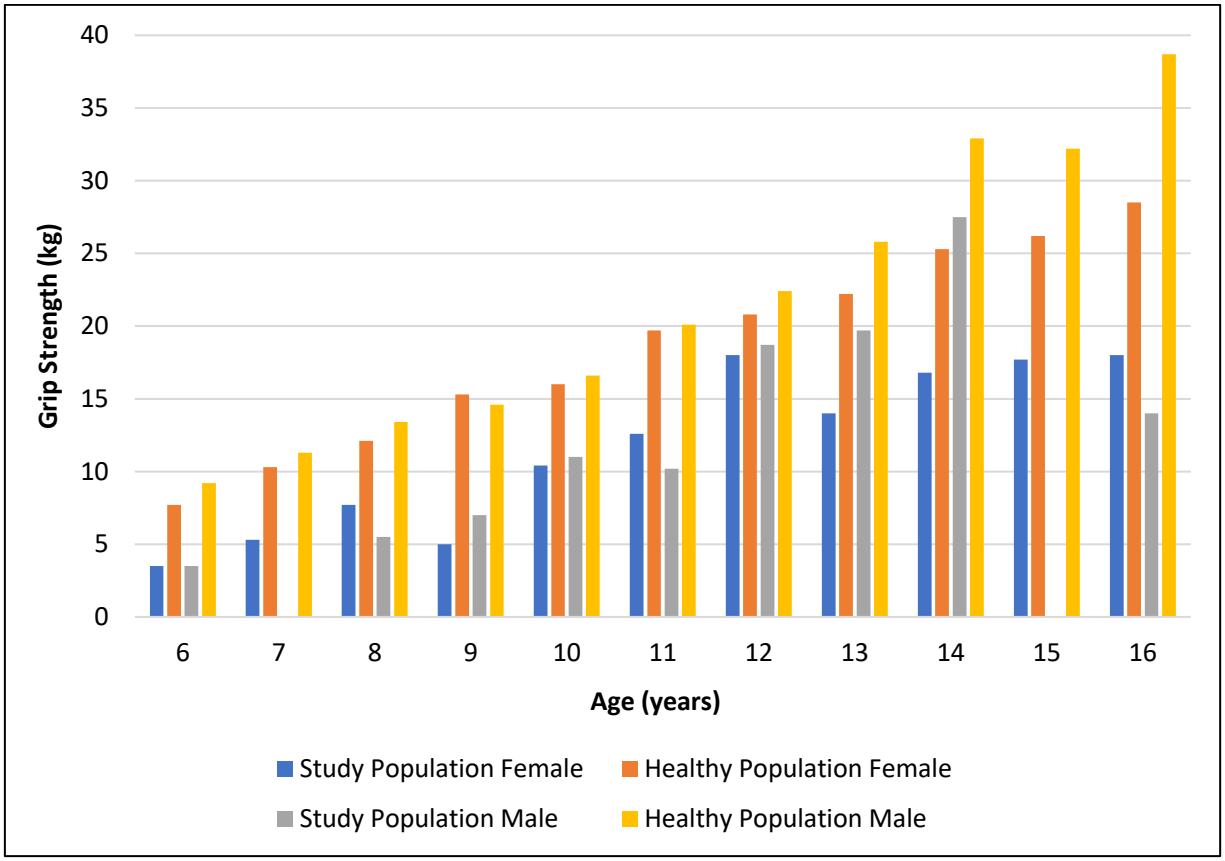


Figure 4.22 Average grip strength in participants and a healthy sample by age and biological sex. There were no study participants in the male 7-years-old, or male 15-years-old categories.

4.11.6.7 Motor skill proficiency

The Bruininks-Oseretsky Test of Motor Proficiency Brief (BOT-2 Brief) was fully completed by n= 79 participants. One participant failed to complete all 12 items of the BOT-2 Brief and was not included in analysis. Mean and SD BOT-2 Brief standard scores for males and females, child (6-9 years) and adolescents (10-16 years) are reported in Table 4.18.

Motor skill proficiency which was below, or well-below average was present in 44.3% (n=35/79) of participants in comparison to age and sex referenced data (232). There was no significant difference between males and females, or between child and adolescent motor skill standard scores.

Table 4.18 Bruininks-Oseretsky Test of Motor Proficiency Brief (BOT-2 Brief) standard scores and percentile rank compared to age and sex specific norms, by biological sex, child, and adolescent subgroups

		Total	Male		Female	
Variable	**n**		**Child (n=7)**	**Adolescent (n=18)**	**Child (n=16)**	**Adolescent (n=38)**
BOT-2 Brief standard score (mean (±SD))	79	42.3 (10.2)	45.1 (9.9)	42.8 (10.8)	43.1 (13.8)	41.2 (8.3)
BOT-2 Brief percentile (median, IQR: Q1, Q3)	79	21 (8, 38)	29 (24, 62)	21 (8, 36)	16 (4, 65)	18 (8, 34)

Data are presented as mean ± SD, or median (IQR: Q1, Q3).

4.11.7 Cluster analysis

4.11.7.1 Missing data and sample size

There was minimal missing data from the features (Y-BT 8 %, n=7/80 missing, BOT-2 Brief 1%, n=1 missing). Complete case analysis was deemed appropriate in this data set as numbers of missing data were extremely small, therefore missing values were not imputed, as described in the methodology.

4.11.7.2 Normality and linearity

Preliminary analyses were conducted on all features to determine any violations of assumptions of normality and linearity. Histograms were inspected and are included in the centre of each scatterplot matrix (Figures 4.23 & 4.24), to observe an overview of normality in each variable. Self-reported physical activity has a slightly skewed distribution to the left (lower physical activity levels), but all questionnaire features appeared to be reasonably normally distributed. Muscle endurance had a non-normal distribution and was heavily skewed to the right (Figure 4.2.4). As expected in this

population, the Beighton score, Lower Limb Assessment Scale, Foot Posture Index were slightly skewed to the right (greater hypermobility and pronated foot posture) and strength was slightly skewed to the left (weaker) (Figure 4.2.4). Functional impairment (6MWD), dynamic balance (YBT), muscle length (popliteal angle) and motor skill proficiency (BT-2BF standard score) were all observed to have normal distributions (Figure 4.2.4).

4.11.7.3 Correlations

Scatter plots and Pearson's correlation coefficient for each pair of features (complete cases only for pairwise comparison) were conducted. If two variables were found to be strongly associated, the cluster model only needed one, as the second would not add any additional information. Correlations (bivariate) between all features were examined (Appendix 28). All relationships were examined using a scatterplot matrix. Figures 4.23 & 4.24 present the scatterplot matrices for two groups: i) between pairs of all questionnaire features (Figure 4.23), ii) between pairs of selected objective measures (Figure 4.24).

The first scatterplot matrix presents four questionnaire features, fatigue (higher scores indicate less fatigue), quality of life (higher scores indicate better quality of life), pain (lower scores indicates less pain) and physical activity (higher scores indicates more physically active) on the x-axis (Figure 4.23).

A significant positive association was found between fatigue and quality of life ($r = .82$, $p < .001$) and fatigue and physical activity ($r = .52$, $p < .001$), and a significant negative association with pain ($r = -.54$, $p < .001$). A significant positive association was found between quality of life and physical activity ($r = .47$, $p < .001$) and a similarly to fatigue, a significant negative association was found with pain ($r = -.57$ $p < .001$). No association was found between pain and physical activity (Figure 4.23).

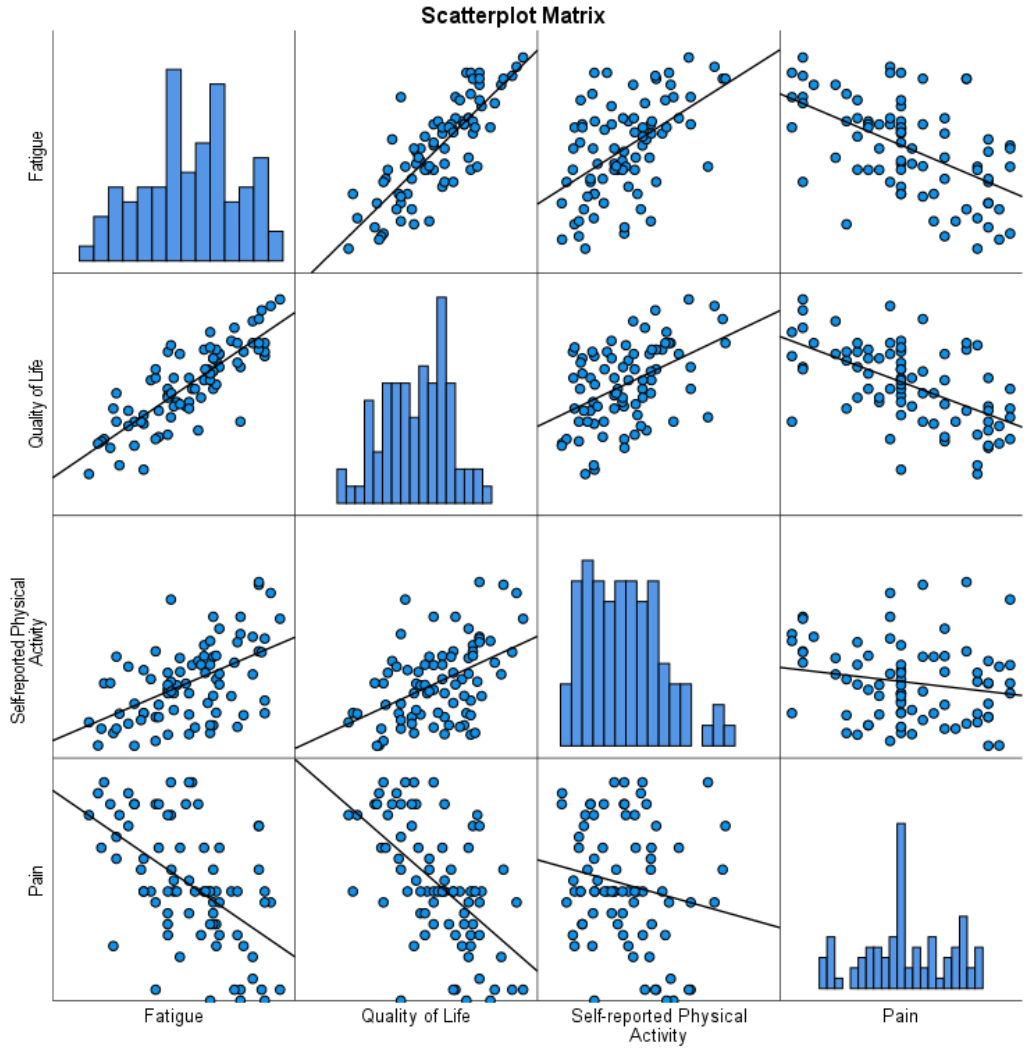


Figure 4.23 Scatterplot matrix and histograms for four questionnaire features: Pain (PedsQL™ Paediatric Pain Questionnaire), Self-reported Physical Activity (Physical Activity Questionnaire), Quality of Life (PedsQL™ 4.0 Generic Core Scale) and Fatigue (PedsQL™ Multidimensional Fatigue Scale)

The second scatterplot matrix consisted of the eight objective features (functional impairment, dynamic balance, strength, muscle length, motor skill, Beighton score, Lower Limb Assessment Scale score and Foot Posture Index) (Figure 4.24). Muscle endurance was not included as it had a non-normal distribution and was not considered as a cluster feature at this stage. The following eight objective features were observed for relationships.

Functional impairment and grip strength were not found to be associated with any objective feature. A significant positive association was found between motor skill proficiency and dynamic balance (r = 0.46, p <.001). A significant positive association between motor skill proficiency and quality of life and fatigue and a significant negative association with pain (r = 0.32 to 0.34, p <0.01).

Measures of connective tissue laxity (muscle length, Lower Limb Assessment scale, Beighton score and Foot Posture Index) were associated with each other; the LLAS and Beighton Score were significantly positively associated (r = 0.39, p <.001), and the LLAS was significantly positively associated with the Foot Posture Index (r = 0.41, p <.001) and Muscle Length was significantly positively associated with the Beighton score (r = 0.34, p = 0.02). However, the Beighton score, Lower Limb Assessment Score and Foot Posture Index were not associated with any other objective feature (correlation coefficients ranged from -0.29 to 0.2). On further investigation with the four questionnaire features, the hypermobility screening measures (Beighton score and LLAS) were not associated with pain, fatigue, quality of life or physical activity levels.

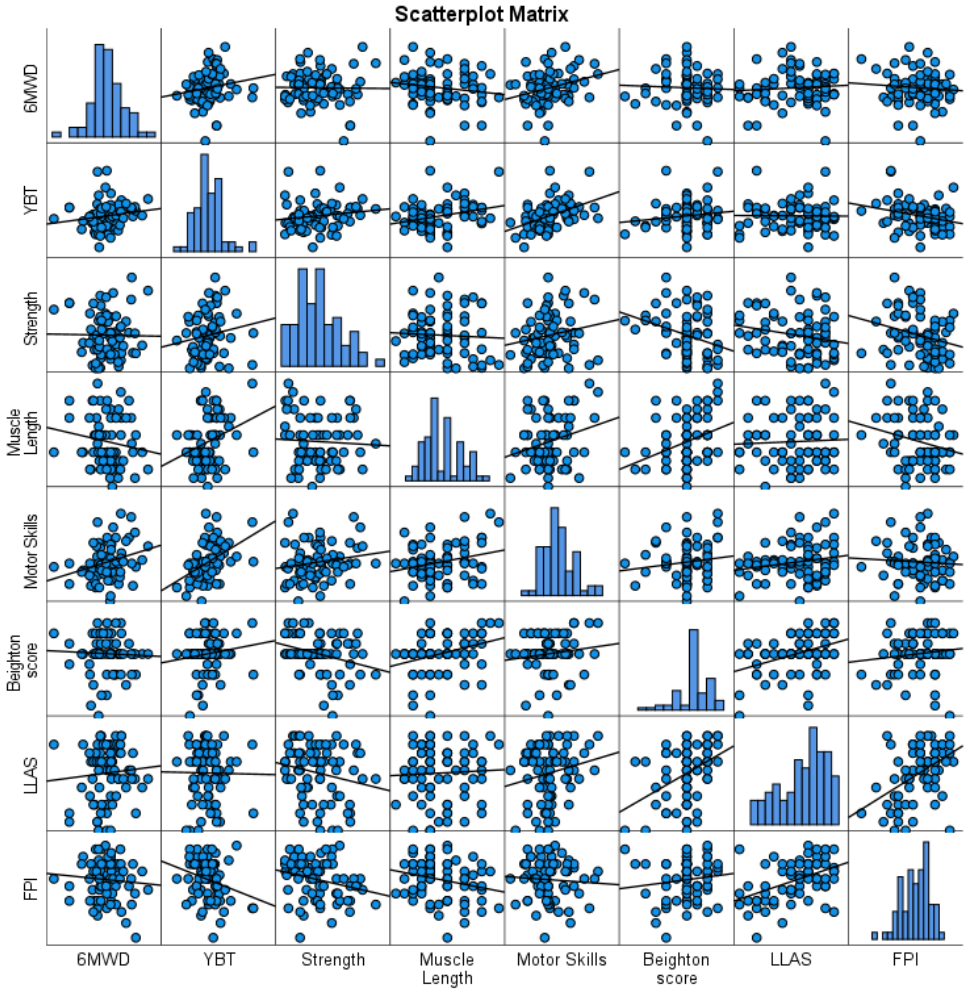


Figure 4.24 Scatterplot matrix and histograms of eight objective features: Functional impairment (6MWD in m), Dynamic Balance (YBT in cm), Grip Strength (strength kg), Muscle length (degrees), Motor Skill Proficiency (BOT-2 Brief standard score), Beighton score, LLAS and Foot Posture Index. 6MWD Six-Minute Walking Distance; YBT Y-Balance Test; BOT-2 Brief Bruininks-Oseretsky Test of Motor Proficiency Brief, LLAS Lower Limb Assessment Scale.

4.11.7.4 Feature selection and feature scaling

The set of cluster features used within the cluster analysis were now selected based upon:

i) reported validity and reliability of each cluster feature,
ii) consideration of normality, linearity, and collinearity, and
iii) consideration of gaussian-distributed features, as one of the distributional assumptions required for this method which involves the calculation of cluster means (218),
iv) previous studies using similar methodologies (76, 85, 86, 116) and finally
v) clinical expertise of Principal Investigator, research team and statistical support team,
vi) Scatter plots and Pearson's correlation coefficient for each pair of features (complete cases only for pairwise comparison) were conducted. If two variables were found to be strongly associated, the cluster model only needed one, as the second would not add any additional information. Correlations (bivariate) between all features were examined (Appendix 28). All relationships were examined using a scatterplot matrix.

The first feature removed from selection was muscle endurance which had a clear non-normal distribution. Secondly, the Beighton score, LLAS and Foot Posture Index were all removed from selection. These features were slightly skewed towards larger values and weak associations with other features. Muscle length was also removed, as it was less clinically meaningful than the remaining features. In terms of the questionnaire features, Physical Activity (self-reported PAQ score) was removed as this measure was less valid and reliable than the other three questionnaire features (Fatigue, Quality of Life and Pain). Finally, Quality of Life was removed, as it was strongly associated with fatigue (collinearity) and therefore including quality of life would not add to the cluster model. Fatigue was chosen to remain instead of quality of life as it was more clinically meaningful in this population. The remaining six features to be considered in the cluster model were fatigue, pain, 6MWD, YBT, strength and motor skills. The remaining features data were standardised to have 0 mean and unit variance (z-score).

4.11.7.5 Development of cluster model

The cluster analysis at this stage focused on the remaining six features. The sample size (n=79) determined that a solution using five features or less, would be appropriate (268). The next stage involved repeated cluster analysis, with different subsets of the six features in different combinations of 5 or less. The results of the scatterplots (Figure 4.23) were also helpful in considering patterns, and correlations amongst features. Each cluster solution was analysed and interpreted theoretically by inspection of each dendrogram, analysis of the similarity coefficient, and by clinical interpretation, knowledge of this clinical area to consider the differences across subgroups. Three features, function and YBT and strength were found to not contribute to the overall separation of the clusters and were therefore removed. The final three-cluster features selected were fatigue, motor skills proficiency and pain. Following further repeated cluster analysis with these three features, a five-cluster solution (Appendix 28) and three-cluster solution were found which could both describe the data (213, 266).

The three-cluster solution (Figure 4.25) was chosen. This was most clinically meaningful, more feasible to implement in practice, and also created clusters large enough to allow for statistical comparison (266). The results were graphically demonstrated using a dendrogram (Figure 4.25).

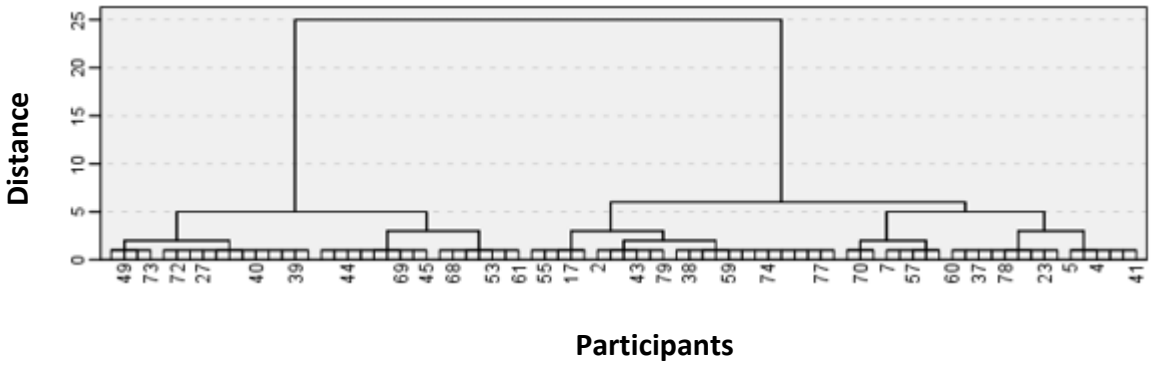


Figure 4.25 Final three-cluster solution dendrogram based on hierarchal clustering. The x-axis indicate individual participants, segments on the height (y-axis) indicate distances where clusters are combined. The three-cluster solution is cut at level 5 on the y-axis.

The resulting clusters (which will now be referred to as subgroups) were given nomenclature to represent their potential clinical pathway, based on their clinical characteristics. The three subgroups were named subgroup 1 – Low Symptom Burden which contained 20.3% (n=16/79) participants, subgroup 2 – Medium Symptom Burden which contained 53.2% (n=42/79) and subgroup 3 – High Symptom Burden which contained 26.6%, (n=21/79) participants. Table 4.19 & 4.20 shows the comparison of categorical and continuous clinical variables across the three subgroups.

4.11.7.6 Composition of subgroups

Figure 4.26 presents the standardised (z-score) mean values for each cluster feature by subgroup. The High Symptom Burden subgroup is characterised by a high mean value across every feature, with the lowest mean motor skill proficiency, lowest fatigue (lower scores indicate worse fatigue) and highest mean pain. Conversely, the Low Symptom Burden subgroup is characterised by a low level of severity in all features, with the highest mean motor skill proficiency. The Medium Symptom Burden subgroup was characterised by low mean motor skill proficiency, but notably less pain, fatigue than the High Symptom Burden subgroup (Figure 4.26).

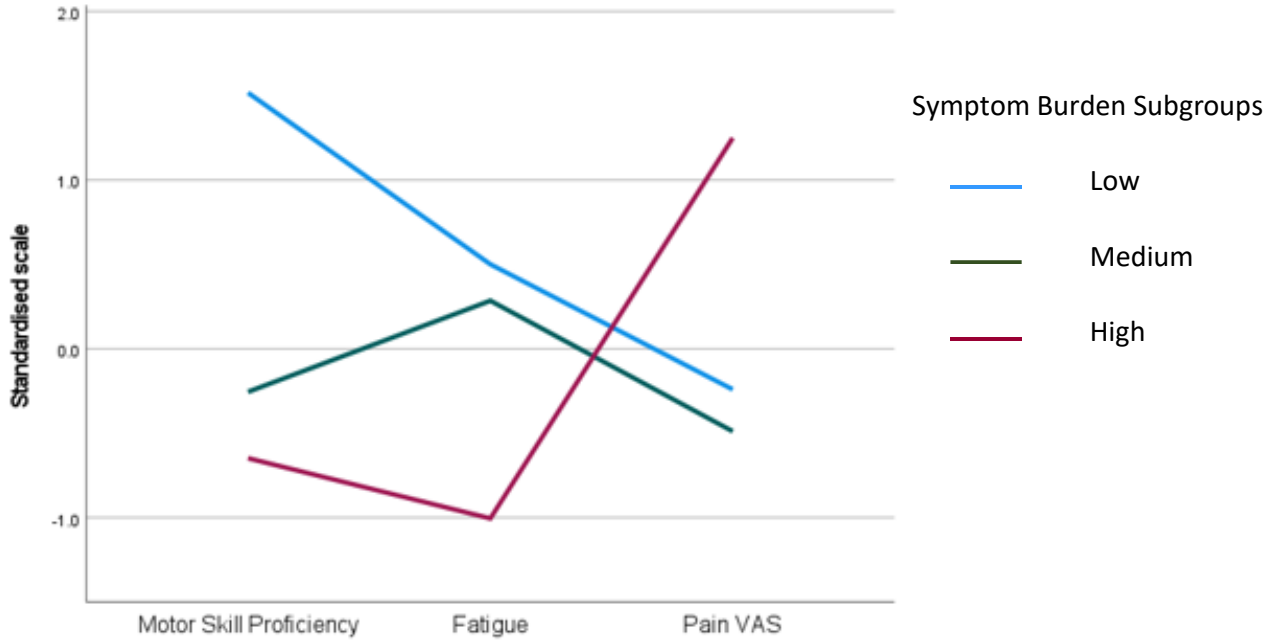


Figure 4.26 Mean standardised values by Low (blue line), Medium (green line) and High (red line) Symptom Burden subgroup. Motor Skill Proficiency (BOT-2 Brief) age and sex adjusted where higher score indicates better motor proficiency, Fatigue (PedsQL Multidimensional Fatigue) where higher scores indicates less fatigue, and Pain VAS (PedsQL Pain Questionnaire) where higher scores indicates higher severity pain

Subgroups were compared across categorical (Table 4.19) and continuous (Table 4.20) clinical variables. A significant difference was found in BMI centiles across the different subgroups (p = 0.03) with participants in the High Symptom Burden subgroup recording significantly higher BMI centiles than participants in the Medium and Low Symptom Burden subgroups. Although the mean age of the High Symptom Burden (M = 12.0, SD =3.2 years) was greater than the Low Symptom Burden (10.7, SD = 3.6) it was not significant (p = 0.39). Post hoc comparisons using the Tukey HSD test indicated that the mean score for the High Symptom Burden subgroup was significantly different from that of the *Medium* and the Low Symptom Burden subgroup in pain (p < .001), fatigue (p < .001), and quality of life (p < .001) (Appendix 28). The mean score for the High Symptom Burden subgroup was significantly different from that of the Low Symptom Burden

subgroup in function (p = 0.03). The Medium Symptom Burden subgroup did not differ significantly from the Low Symptom Burden subgroup in pain (p = 0.39) fatigue (p = 0.63) or quality of life (p = 0.91). The High Symptom Burden subgroup did not differ significantly from the Medium Symptom Burden subgroup in motor skill proficiency (p = 0.05).

The percentage of participants with self-reported Developmental Co-ordination Disorder was equal in the Medium Symptom Burden subgroup and the High Symptom Burden subgroup. Participants in the Low Symptom Burden subgroup had a higher mean PAQ (2.7) than both the Medium Symptom Burden (2.4) and High Symptom Burden (2.1) subgroup, which were both under the cut-off of 2.7, used to discriminate between active and inactive children (241). A higher percentage of ASD and/or ADHD diagnosis (self-reported) were represented in the High Symptom Burden subgroup (n=6, 29%), compared to the Medium Symptom Burden subgroup (n=5, 12%) and the lowest reported in the Low Symptom Burden group (n=1, 6%) (Table 4.19).

Table 4.19 Comparisons of categorical variables by Low, Medium and High Symptom Burden subgroups.

Demographics and clinical characteristics	**Total n (%)**	**Low** Symptom Burden **n (%)**	**Medium** Symptom Burden **n (%)**	**High** Symptom Burden **n (%)**	***p*-value**
n	79 (100)	16 (20)	42 (53)	21 (26)	
Females	54 (67.5)	12 (75.0)	24 (57.1)	18 (85.7)	0.06
Orthostatic intolerance	32 (40.5)	4 (25.0)	18 (42.9)	10 (47.6)	0.3
Urinary incontinence	15 (19.0)	2 (12.5)	5 (11.9)	8 (38.1)	0.04*
Joint Instability	21 (26.6)	3 (18.8)	11 (26.2)	7 (33.3)	0.08
Gastrointestinal Reflux	10 (12.7)	1 (6.3)	5 (11.9)	4 (19.0)	0.4
Skin (mildly hyperextensible/doughy, presence of atrophic scar or unexplained striae)	14 (17.7)	0 (0)	9 (21.4)	5 (23.8)	0.1
Developmental Co-ordination Disorder	18 (22.8)	0 (0)	12 (28.6)	6 (28.6)	0.03*
ASD/ADHD [¥]	12 (15.2)	1 (6.3)	5 (11.9)	6 (28.6)	0.1
Below average motor skills [#]	35 (44.3)	1 (6.3)	18 (42.9)	16 (76.2)	<.001*

[¥] ASD Autistic Spectrum Disorder, ADHD Attention Deficit Hyperactivity Disorder self-reported in structured interview and verified in medical chart review; [#] Motor skill proficiency measured by BOT-2B compared to age and sex matched normative data, n = 79 as one participant did not complete the test. BOT-2 Brief Bruininks-Oseretsky Test of Motor Proficiency Brief. * significant at 0.05 level. Data are presented as frequency (percentage).

Table 4.20 Comparison of continuous variables by Low, Medium and High Symptom Burden subgroups.

Demographics and clinical characteristics	**Total**	**Low** Symptom Burden	**Medium** Symptom Burden	**High** Symptom Burden	***p*-value**
n	79 (100)	16 (20)	42 (53)	21 (26)	
Age, years	11.6 (3.0)	10.7 (3.6)	11.7 (2.6)	12.0 (3.2)	0.39
BMI centile	59.82 (29.1)	55.4 (30.1)	54.3 (29.7)	74.3 (23.0)	0.03*
Length of time to diagnosis, months (median, IQR)	24.0 (12.0, 48.0)	24.0 (12.0, 24.0)	24.0 (12.0, 48.0)	24.0 (12.0, 48.0)	0.1
Beighton score (median, IQR)	6.0 (6.0, 7.0)	6.5 (6.0, 8.8)	6.0 (5.5, 6.3)	6.0 (6.0, 7.0)	0.33
LLAS (median, IQR)	7.0 (5.0, 9.0)	8.0 (6.3, 10.0)	7.0 (4.0, 9.0)	7.0 (2.5, 9.5)	0.22
Foot Posture Index	6.9 (2.6)	6.9 (2.7)	7.1 (2.8)	6.6 (2.2)	0.75
Muscle Length	146.1 (13.9)	153.1 (17.8)	143.6 (11.5)	145.7 (13.9)	0.06
Pain VAS [a]	5.3 (2.8)	4.7 (2.2)	4.0 (2.0)	8.8 (1.0)	<.001*
Fatigue [b]	56.9 (21.9)	68.2 (18.5)	63.4 (18.1)	35.2 (15.8)	<.001*
Motor skill, BOT-2 Brief	42.3 (10.2)	57.8 (6.3)	39.7 (6.7)	35.7 (5.7)	<.001*
Quality of Life [b]	60.2 (18.2)	67.8 (14.9)	66.0 (16.0)	43.1 (13.6)	<.001*
Functional impairment, 6MWD m	518.2 (91.6)	550.5 (76.6)	527.8 (86.9)	474.8 (99.2)	0.03*
Dynamic balance, YBT cm [e]	100.3 (13.0)	106.8 (11.7)	99.3 (14.6)	96.8 (7.7)	0.03*
Muscle endurance (median, IQR) [f]	51 (30.0, 120)	105 (42.3, 120)	52.0 (39.3, 120)	34 (16.5, 120)	0.07
Strength, Grip strength kg	10.5 (6.3)	10.6 (6.6)	10.3 (6.2)	10.7 (6.3)	0.9
Self-reported Physical Activity [g]	2.4 (0.7)	2.7 (0.8)	2.4 (0.7)	2.2 (0.6)	0.1

[a] 0-10 where higher scores indicate worse pain; [b] 0-100 where higher scores indicate less fatigue and better quality of life; [c] Motor skill standard score where scores <31 indicate below average motor skills; [d] 6MWD measured in metres; [e] normalised to leg length, n = 73 as seven participants did not complete the YBT; [f] Straight leg lift measured in seconds; [g] Self-reported physical activity levels. BMI Body Mass Index; LLAS Lower Limb Assessment Scale; VAS visual analogue scale, BOT-2 Brief Bruininks-Oseretsky Test of Motor Proficiency Brief. * significant at 0.05 level. Data are presented as mean ± SD, unless otherwise specified, where median and IQR (Q1, Q3) are presented.

4.12 Discussion

This study found that children and adolescents with symptomatic hypermobility have worse quality of life, fatigue, function, strength, and endurance than healthy paediatric populations. Additional diagnoses were common, significantly, a high level of neurodevelopmental diagnoses, and BMI centiles were comparable to similar school age children in Ireland (272). Development of more comprehensive clinical profiles could assist clinicians in planning appropriate clinical pathways in order to address symptoms incorporated in a biopsychosocial model of care. An aim of this study was to identify if subgroups could be identified using appropriate cluster analysis. It was hypothesised that homogenous subgroups could be identified using subjective and objective clinical measurements. Three subgroups were identified using cluster analysis of systematically selected features: Low Symptom Burden, Medium Symptom Burden and High Symptom Burden. These subgroups were identified using valid and reliable clinical measures, feasible in a clinical environment, contributing to the utility of the measures. Whilst the nature of this study was exploratory, and further research and validation is required, the identification of three subgroups is meaningful, and could be of interest to clinicians. The subgroups may inform the future development of targeted interventions aimed at improving the treatment efficiency in patients with symptomatic hypermobility. Furthermore, the results of this study were integrated into the following qualitative study (Study III) to gain novel insights into the results, which will be reported in the final chapter of this thesis.

4.12.1 Feasibility

This study found that the testing protocol was feasible to carry out in children and adolescents. This was demonstrated following a feasibility study with three healthy school-aged children, where timing and the length of overall testing were found to be important considerations. In light of this, a specific order of testing was designed, to maximise position changes throughout the testing.

With the exception of dynamic balance as measured by the YBT and motor skill proficiency as measured by the BOT-2Brief, 100% of participants completed each clinical

measurement during the testing phase of the study. The YBT was not completed by seven participants, and the BOT-2BF was not completed by one participant. The YBT has been used in previous studies in children and adolescents with hypermobility (85, 116), however it is unclear whether the standardised protocol of nine trials (six practice and 3 test) was used. In this study, the participants who did not complete the YBT were mostly younger participants. This may have contributed to the inability to complete the test. However, a previous study using the YBT in children with DCD, with similar age participants, and followed the standardised protocol, did not report any dropouts (273). The large symptom burden and number of additional diagnoses in this cohort may have affected to the dropout rate in this particular measurement and should be a consideration to the feasibility of the YBT in younger children with symptomatic hypermobility.

4.12.2 Pain

In the present study, chronic pain was present in 100% (n=80) of participants, with 62% of participants reporting pain in 3 sites or more, most commonly in the lower limb (95%) specifically, in knee joints (72.5%). In study I of this thesis (210), musculoskeletal clinical characteristics including chronic recurrent pain, were the most common characteristic in children, adolescents and young adults with symptomatic hypermobility. Chronic musculoskeletal pain has been documented as a clinical feature since the earliest reports of joint hypermobility and musculoskeletal complaints in the scientific literature (64).

The aetiology of pain in symptomatic hypermobility is not clear, and Feldman et al., 2020 (69) proposed that current theories may not be mutually exclusive and that in the context of joint instability, with repeated injuries, or microtraumas, repeated nociception and central sensitisation may be interdependent (69). As pain is defined as “an unpleasant sensory and emotional experience with or resembling that associated with, actual or potential tissue damage, or described in terms of such damage” (274) the assessment of factors beyond the biological components of pain is essential to understand the child or adolescent’s pain experience.

Multisite pain (94%) occurring mostly in the lower limb (88%) and commonly the knee joint (63%) was also reported by Pacey et al., 2015 (85) in an Australian cohort of 6–16-year-olds with symptomatic hypermobility (JHS). Similar pain severity, with multisite pain was reported in a later Australian study of n=101 6–16-year-olds with symptomatic hypermobility (JHS/EDS-HT) (116). This was in contrast to a cohort from the UK reporting much lower pain severity (21). Waiting times for assessment were not reported, which may have impacted pain reports. Similar to the current study, both Australian cohorts were recruited from tertiary settings (connective tissue dysplasia clinic, rheumatology, sports medicine, and other settings) whereas the UK cohort were recruited from primary and secondary settings (community and general paediatrics, orthopaedics, physiotherapy and occupational therapy and general practice). The care pathway, or waiting times to access a tertiary service, may be a factor in pain presentations.

Chronic pain is also common in the general population (68, 275). The prevalence of chronic pain amongst adolescents varies but a large population study in 42 countries reported that self-reported chronic pain is common, with 44.2% of adolescents reporting chronic weekly pain during the last 6 months, more commonly in females and older age groups (275). Although limited to headache, backache and stomach-ache, the prevalence of multisite pain (chronic pain in at least two of these sties) was found to be 16.9% in an Irish cohort of adolescents with a significantly greater prevalence in females (20.5%) compared to males (11.1%) (p>.001) (275). The high prevalence of chronic multisite pain reported in participants in Study II of this thesis, in comparison to the general population is of concern, as chronic pain in childhood is associated with pain in adulthood (276).

WHO guidelines for chronic pain in children, define chronic pain as ‘pain that persists or recurs for longer than three months’ (277). Chronic pain is categorised as Chronic Primary Pain, and Chronic Secondary Pain (277). Chronic primary pain can be diagnosed independent of identified biological or psychological contributors, and describes pain characterised by significant emotional or functional disability (277). Chronic Secondary Pain has a clear underlying aetiology and is divided into seven categories, which include chronic secondary musculoskeletal pain (68). In situations with joint instability, subluxation or dislocation, a diagnosis of Chronic Secondary Pain could be useful to help

to target care. The degree of hypermobility was not associated with the level of severity of pain in this study. Other pain mechanisms such as generalised hyperalgesia which may indicate involvement of the central nervous system have been proposed, which may be a result of ongoing pain, or could be a combination of repeated musculoskeletal injury and up regulation in the central nervous system (115). The possibility of heightened pain-related fear is also proposed as a mechanism to understand the relationship between symptomatic hypermobility and disability (152). There is growing evidence that patients with chronic pain show a reduced ability to learn threat, and safety signals (278). Our stress system is more easily offset by situations that we learn are threatening, and less triggered by situations that are understood as harmless (278). The recognition of hypermobility starts with an exclusion of rare, often serious genetic conditions, which can be associated with hypermobility (279). Ongoing uncertainty, poor recognition, and lack of defined clinical pathways to management, may contribute to a level of stress, and threat, which could also contribute to the development and maintenance of chronic pain in symptomatic hypermobility. Given the high prevalence of chronic pain in this population, pain assessment should be a key element of a clinical assessment, using WHO classifications to help patients and parents to better understand pain mechanisms, using the biopsychosocial approach, as recommended by the WHO (68). The High Symptom Burden subgroup exhibited greater pain severity scores, higher painful site count, and a higher medication count. Managing chronic pain in childhood is complex and challenging for clinicians, and this group could be targeted for more intensive resources focusing on the interdisciplinary management of complex pain (277).

4.12.3 Fatigue

Participants in this study had higher levels of fatigue than a healthy population, and higher levels of fatigue than children with other chronic conditions (280). Mental fatigue subscales were worse in comparison to general and sleep/rest fatigue subscales, and adolescent females reported the highest levels of overall fatigue. The association of chronic fatigue syndrome (CFS) with hypermobile EDS in a small sample of adolescents (n=6, median age 15.5), was first reported over twenty years ago (138). Since then,

several studies have identified the presence of fatigue in children and adolescents with symptomatic hypermobility (87, 116, 148, 153, 155). Fatigue was the principal complaint in 17 out of 30 adolescents with symptomatic hypermobility (BJHS) recruited from paediatric and rheumatology clinics (153). At-risk, or clinically significant fatigue was highly prevalent in n=34 paediatric hEDS patients, with 50% also reporting insomnia, with n=5 participants reporting that fatigue was the 'hardest thing' about having hEDS (155). Data from this current study identified a strong relationship between fatigue and quality of life, which is well documented in the literature (87, 281).

Possible mechanisms driving fatigue in this population, similarly to pain, are likely to be multifactorial (282). Exploring the physiological mechanism in adults with symptomatic hypermobility (JHS) in comparison to a control group, participants with JHS felt greater fatigue, and exhibited central fatigue which did not occur in the control group (282). Paediatric studies exploring mechanisms of fatigue in this population are lacking. Assessments for children and adolescents with symptomatic hypermobility have focused largely on outcomes of pain and function (21, 124, 149). Increased awareness of the presence of fatigue and sleep issues especially into adolescence, could help to target management, which may require a more paced approach to management, especially exercise (244).

4.12.4 Motor skills

In this study, 44% of participants were categorised as having below or well below average motor skill proficiency. Similar findings of poor motor skills have been reported in children with symptomatic hypermobility in tertiary settings and to a lesser degree in primary care health settings, although different methodologies limit direct comparisons (133, 283). Current evidence for conservative management of patients with symptomatic hypermobility, focuses on exercise as a core component (83), therefore achieving proficiency in motor skills, is essential to engage in exercise interventions (284).

The prevalence of reported Developmental Co-ordination Disorder (DCD) in this study was 23.8%. This is far greater than the estimated prevalence of 5-6% in children aged 5-

11 as defined by standardised testing using the DSM-IV criteria (285). A high prevalence of generalised hypermobility has been reported in children with DCD (286, 287). However, there is a lack of consensus in the literature, with some studies reporting no observed association (49) and others finding a high rate of neurodevelopmental disorders including DCD (288) although different methodologies limit comparison. Proprioceptive impairment has been proposed as a possible factor for individuals with generalised hypermobility who develop DCD, but whether there is a cause-effect progression is still unclear (169). Interestingly, this research used cluster analysis to identify subgroups, which differed by rates of DCD and motor skill proficiency, which could help to target interventions. Screening motor skills and neurodevelopmental diagnoses such as DCD are recommended using standardised assessments. Increased communication between different settings is also required, as assessments are often conducted in primary care settings, to enable clinicians in tertiary settings to better triage patients to direct their care.

4.12.5 Muscle strength and endurance

In this study, strength and muscle endurance, were significantly weaker compared to age and sex normative data for all ages (231). Strength deficits have previously been reported in paediatric hypermobility populations (66, 127). Only 31.3% (n=25/80) of participants achieved the maximum straight leg raise of 120 seconds, used to measure endurance, compared to 96% of healthy children (250).

Typical youth are weaker than previous generations, which emphasizes the importance of strengthening in this cohort who present significantly weaker than a healthy population sample (284). A recent randomized controlled trial in adult patients with shoulder pain and symptomatic hypermobility, demonstrated that high load strengthening could be used to improve function and reduce symptoms (289). Further studies are required in the paediatric setting. Implementing conditioning could be particularly important for this cohort, compared to other paediatric chronic pain cohorts. Improving strength forms the foundation for movement, and participation in sports and activities (290). Children and

adolescents with additional diagnoses such as neurodevelopmental disorders, will require a more targeted approach.

4.12.6 Physical activity

The mean PAQ score for males (2.7) and females (2.2) in this study were lower than cut-off values (male 2.9 and female 2.7) defined as 'sufficiently active' (240). Objective measures are preferential in the measurement of physical activity in children, however self-reports can also be helpful assessing sport type, engagement in physical education, and activities during free time like yard, and after school (240). In agreement with normative data in a large sample of males and females in the UK, the mean PAQ scores in this study were greater in males than females (240). Females in this study also had lower mean PAQ scores than a cohort of Irish females (n=35) of a similar age with an inflammatory diagnosis of Juvenile Idiopathic Arthritis who were also found to be less active than their peers (242). The most popular activities in this cohort were walking and swimming followed by Gaelic football, indicating a preference for individual activities over team sports (63% vs 37%).

4.12.7 Functional impairment

Participants had significantly worse six-minute walking distance compared to a sample of healthy age and sex matched population (248). Mean 6MWD were slightly higher than a study with a similar cohort (291), although the mean age was older, and this is a significant predictor of the 6MWD (248). A recent study reported a significant improvement in 6MWD following the use of custom-made orthotics over a 3-month time period (291), which offers some evidence for the use of orthotics to improve function in this cohort. Assessing physical functioning is recommended in paediatric chronic pain interventions (212) and by a systematic review in children with symptomatic hypermobility (211).

4.12.8 Hypermobility, muscle length and foot posture

In this study, a higher degree of hypermobility was not found to be associated with any of the subjective measures of pain, fatigue, quality of life or physical activity levels, or objective measures of function, balance, strength, and motor skills. As this study, including most studies describing the association between hypermobility and symptoms are cross-sectional, causality remains unknown (156). There is some higher quality evidence associating generalised hypermobility with a higher risk of injury (292), which was not assessed in this study. A prospective observational registry study has reported that patients with generalised hypermobility participating in competition level sports have a 5.53-fold greater risk of a second ACL injury within 12 months, than those without generalised hypermobility (292).

Further studies using strict cut-offs, standardised assessments, and longitudinal designs, controlling for confounding factors, are needed to help to understand the effect of generalised hypermobility in the development of symptoms. Targeting motor skills in children and adolescents with generalised hypermobility may play an important role in prevention of soft tissue injuries into later adolescence and early adulthood, to ensure a life-long participation in activity.

In this study, generalised hypermobility was screened by the Beighton score and Lower Limb Assessment Scale as both are valid and reliable in paediatrics (54). The recently revised diagnostic framework for paediatric rheumatology recommends using the Beighton score with a cut-off of ≥6/9 to screen for generalised hypermobility (6). Children without generalised hypermobility were included in the current study if they were deemed to have symptomatic hypermobility in the paediatric rheumatology setting. Paediatric Rheumatologists use a pGALS (81) and PREMS (80) assessment approach to examine a child's musculoskeletal system. This structured examination assesses active and passive joint range in every joint, to exclude other causes of joint pain, such as inflammatory arthritis (80) and can identify hypermobility if the clinician has an awareness of typical joint range.

The Beighton score was positively associated with the LLAS and hamstring muscle length. Muscle length has been used as a measure of connective tissue laxity in previous studies

(116) and was significantly greater in females than males in this study. Mobility deficits in hamstring length presenting with higher-than-normal foot posture may represent a group that can be targeted for management similarly to those presenting with patellofemoral pain (216).

Using standardised protocols and goniometry are recommended to recognise hypermobility in the child (54). Age, biological sex and ethnicity are known to influence joint range, and therefore normative scales are needed taking all these factors into consideration (55). Clinician expertise and judgement were deemed important in this study, as has been argued by Malek et al. 2021 (55) to ascertain the impact of hypermobility on presenting symptoms. Recognition of symptomatic hypermobility in this study, occurred following a skilled, systematic, screening process in the paediatric rheumatology clinic. Expertise in musculoskeletal assessment is important when using this approach, and support and training for clinicians outside of musculoskeletal settings is essential to ensure not only early recognition, but avoidance of over, or under recognition of paediatric hypermobility. Future research including qualitative research, could be helpful to investigate clinicians' experience of using either tool in a clinical scenario and explore clinicians' beliefs in different paediatric settings.

4.12.9 Additional diagnoses and multisystemic complaints

Additional diagnoses were extremely common in participants, with 90% reporting the presence of at least one. Associations between paediatric hypermobility, additional diagnoses and multi-systemic complaints such as chronic primary pain, persistent fatigue, dysautonomia and many others, are hampered by heterogeneity across diagnostic criteria and outcome measures, and lack of higher quality study designs. The high percentage of additional diagnoses in this study may be due to recruitment from a tertiary centre and long waiting times (median, IQR Q1, Q3: 24 months, 12months, 48months). Similar reports of symptomatic gastroesophageal reflux were found in data extracted from n=318 case notes of children with symptomatic hypermobility (86). Other studies reported higher percentages of gastrointestinal involvement (54%) and stress incontinence when coughing, sneezing or during physical activity (39%) self-reported

during a clinical exam (87). These reports are greater than those found in the current study where medical charts were reviewed to verify self-reported additional diagnoses. Using standardised diagnostic criteria across multiple clinical domains may be difficult to conduct in specialised tertiary settings and may require several onward referrals for specialised assessments. Further research is needed to investigate associations between hypermobility and other conditions, as this may help better understand potential mechanisms, and also affects treatment pathways for patients and families.

4.12.10 Quality of life

Children and adolescents with symptomatic hypermobility were found to have worse quality of life than healthy children, and lower scores than children with other chronic conditions including studies of children with chronic cardiac conditions (234) and survivors of childhood tumours (235). Mean scores corroborate other studies which demonstrate similar findings (85, 87, 116, 148, 291). Quality of life was strongly associated with fatigue and negatively associated with pain. Pain, fatigue and urinary incontinence were found to account for 75% of the variance in child reported quality of life (87), and in a study using the same measure, fatigue and pain were the main predictors of child reported quality of life, accounting for 90% of the variance (148). Hence, addressing pain and fatigue is important to improve quality of life.

4.12.11 Biological sex

In this study, the sample contained more females (n=54/80, 67.5%) compared to males. This is a similar trend to other studies (74). It has been proposed that there may be a gene-environment interaction (1). The more likely explanations are that genetic, developmental, functional and environmental factors are all at play (1). In this study, females presented with significantly worse quality of life, fatigue, and were less physically active than males. Whilst females reported greater pain than males in this study, levels did not reach significance. Population studies have demonstrated that adolescent females have been found to be at particular risk of chronic pain, increasing with age

(293). The role of sex hormones which may affect symptomatic conditions more common in females, such as irritable bowel syndrome (294) and migraine headaches is evident in the literature (295). Sex differences in pain perception, and sex differences in the musculoskeletal system including muscle tone, tendon and ligament stiffness may contribute to reduced symptomatic presentations and point to 'protective' factors which may influence clinical expression in males (295).

4.12.12 Cluster analysis and clinical subgrouping

This study identified three clinically meaningful subgroups. The High Symptom Burden subgroup exhibited the greatest severity across all clinical variables. The high symptoms burden group present with a complex clinical presentation which requires an Interdisciplinary-led, and more intensive management approach. This group may require more monitoring over time as features may evolve. The Medium Symptom Burden subgroup is mainly characterised by reduced motor skill proficiency compared to children of similar age and sex. Unlike the High Symptom Burden subgroup, this group have less pain and fatigue and better quality of life scores. Participants in the Medium Symptom Burden subgroup and the High Symptom Burden subgroup had a similar percentage of participants with DCD (29% in each subgroup). Clinically, the Medium Symptom Burden subgroup have less complexity, and the focus of management would be directed towards improvement of strength and motor skills (290). It would be of great interest to see if this Medium Symptom Burden subgroup progresses into the High Symptom Burden group over time, and if this is the case, early intervention at this lesser complex stage is essential.

The Low Symptom Burden group is characterised by better scores across the main outcome measures of pain, fatigue, quality of life, and function. With less symptoms, their care needs are lower, and simple management may suffice. This group have the highest physical activity scores, but with mean age on the cusp of adolescence, it would be of interest to see if these are maintained, and to investigate if/how symptoms evolve over time.

Three cluster features pain, fatigue and motor skill proficiency were found to be most reliable in identifying the clinically meaningful subgroups. This is in contrast to previous literature, which identified that the COMPASS-31 questionnaire as most reliable feature in clustering, albeit in a group of adults (76). The COMPASS-31 is a self-assessment questionnaire which assessing autonomic symptoms across multiple domains but primarily validated for use in adults, therefore was not considered for use in this current study (296). In paediatric studies, different methodologies limit comparison between studies. Five distinct subtypes were proposed by Pacey et al., 2015 (85). Participants were recruited in more varied settings, and a large number of variables were used in the factor analysis (85). The high prevalence of skin involvement (78%) compared to this study (17.5%) may be accounted for by the different methodologies used during data collection. Two subgroups 'athletic-persistent' and 'systemic-profound' were proposed by a later study (86). Interestingly there were more older females in the 'athletic-persistent' group who had less pain and were more active, and more males of a younger age in the 'systemic-profound' group with more hypermobility, pain, and multi-system involvement, which is at odds with the findings of the current study (86). There were more females in the Higher Symptom Burden subgroup in the current study, although this did not reach significance (p = 0.06). Participants in the Higher Symptom Burden subgroup had significantly more pain, fatigue and multi-system involvement compared to the Medium and Low Symptom Burden subgroups.

Cluster analysis has been applied in other areas where heterogeneity exists within disease populations, such as patellofemoral pain (17), irritable bowel syndrome (214) and asthma (218). Selecting the appropriate number of clusters can be challenging (213, 218). The dendrogram was used as a graphical technique to visualise the potential number of subgroups (213). However, a key determinant in choosing the number of clusters in this current study was the clinical interpretation of each solution. A novel design was used in this research, to connect the subgrouping findings in this quantitative study, with the following qualitative study, to gain further insight into subgrouping using a qualitative methodology. The integration of these two studies will be discussed in Chapter 6.

4.12.13 Targeted management

Currently, physiotherapists have a central role within the multidisciplinary management of paediatric patients with symptomatic hypermobility (20) However, evidence is sparse, mostly focused on single modal physiotherapy interventions, and lacks high quality study designs (20, 124, 157). One multidisciplinary (physiotherapy and occupational therapy) study found little benefit from an intensive MDT approach but commented that there may be subgroups which would benefit from such an approach (21). Previous literature has identified that children and adolescents with symptomatic hypermobility who present with a greater incidence of multi-systemic complaints, high levels of pain and fatigue are more likely to deteriorate and warrant clinical prioritisation (116). Identifying risk profiles (20), and those with greater clinical needs, including those with greater complexity, could also help to direct care. This care could be led by an Interdisciplinary model of care. Those with lesser complexity may be appropriate for the more traditional physiotherapy-led exercise intervention. Future research including randomised controlled trials could be conducted to determine if subgrouping combined with more targeted treatment is better than best current care, at reducing disability in children and adolescents with symptomatic hypermobility.

4.12.14 'Ladder' of care

Targeting management to clinical subgroups could direct health care and optimise resources, to improve patient outcomes. As symptoms have been proposed to evolve over time (91), care needs may also change over time, providing the need for a 'ladder' approach. This type of approach has been used in other areas of medicine, such as pain management (analgesia ladder (297)), or paediatric allergy (milk ladder (298)). Using a ladder approach, interventions could be increased or decreased, as symptoms change over time. Resources are targeted according to subgrouping. This could lead to a more structured care pathway approach for this cohort of patients.

4.12.15 Limitations

A number of limitations of this study warrant acknowledgement. The final sample size recruited in this study, is smaller than original estimations included in ethics applications, and the study design phase. The sample may limit the stability of the final clustering; however, the clinical interpretability is high and future research is planned to test the stability of the clusters in an independent sample.

Additional diagnoses were self-reported, but they were verified in the medical chart. Using standardised assessments for neurodevelopmental disorders and mental health conditions was not feasible in this study. These assessments are often conducted in primary or secondary settings. Future use of electronic health records may improve the communication between different settings which may assist clinicians having more awareness of additional diagnoses carried out in other settings. As mental health symptoms often co-occur with chronic pain, in particular into later adolescence, screening questions, which are followed up by referral to appropriate services are warranted.

This study used the BOT-2Brief, a shortened version of the full version (BOT-2) to screen for motor skill proficiency (256). However, it was found to be feasible, as part of the Battery of Testing used in the study. Additionally, the BOT-2Brief uses minimal space, low-cost equipment and is quick to carry out (12-15 minutes) (256). It has been shown to be reliable and valid in similar populations (255, 258, 299).

Physical activity levels were not measured objectively. Harnessing digital and wearable technologies could improve the quality of data collected and should be applied in future research. However, wearables were not feasible in this study, and the use of the valid and reliable physical activity questionnaire did provide useful information with regards behaviours and activity type (226, 238).

4.12.16 Impact of Covid-19 and Cyber-Attack on Study II

There have been two significant events which impacted data collection in Study II.

1. The Covid-19 pandemic had a significant impact on Study II. Following public health advice, the number of staff, patients and parents attending CHI sites was dramatically reduced. Attending a clinical site was determined by clinical need and priority was given to patients with the most acute needs, one parent only attending, and staff rostered to allow for social distancing on site. As a direct result: i) the feasibility study was conducted in a safe setting outside of a clinic site; ii) the number of potential participants that could be recruited to Study II was dramatically reduced during 2021; iii) ethics amendments were written to reflect changing circumstances; and iv) additional meetings were required with clinical staff to discuss constantly changing policies and protocols.

2. The cyber-attack to the HSE (Health Service Executive) (May 2021) coincided with the onset of this study's data collection period (July 2021). This incident immediately resulted in loss of access to all IT systems within the HSE hospital systems in Ireland - including medical chart access, labs, and other clinical care systems (39). Rheumatology clinics in Children's Health Ireland (CHI) were severely disrupted for a number of months following the cyber-attack. As a result, the number of patients attending clinics was significantly reduced, and subsequently, the numbers of patients eligible for inclusion to this study was also significantly reduced.

4.12.17 Generalisability

Children and adolescents were recruited from tertiary paediatric rheumatology clinics. This may not be representative of the wider cohort of children and adolescents with symptomatic hypermobility who present to primary or secondary services. However, there is only one tertiary centre in Ireland, therefore participants were representative of both rural and urban settings across Ireland. Ethnicity was largely Irish white. This study included a small number of other white (eastern Europeans) and Asian participants. Accessing other ethnicities is important, as this has been found to be a factor in the prevalence of hypermobility. Conducting research in more diverse ethnicities may help to further explore protective, or predictive factors in other populations.

4.12.18 Clinical relevance of the findings

Education, advice, and management targeted in the primary care or community setting is more appropriate for the Low Symptom Burden subgroup. Children and adolescents in the Medium Symptom Burden subgroup lacking proficiency in motor skills and strength, should have specific, targeted strengthening with a focus on movement in a safe and fun environment with a long-term goal of fundamental movement skill proficiency and improved participation in sports and activities (290). Those presenting in the High Symptom Burden subgroup, with the highest needs, should be referred and managed by the Interdisciplinary team.

4.12.19 Summary

The clinical characteristics of the study population were explored, using a robust methodology which included medical chart review, questionnaires, and a structured interview with both the study participants and their parent/guardian. This was followed by nine objective measures which identified symptomatology across broad clinical domains. Children and adolescents with symptomatic hypermobility reported significant pain and fatigue and had poor quality of life compared to other children with chronic conditions. Participants were not sufficiently active, with reduced function, strength and endurance compared to age and sex normative data. Motor skill proficiency was reduced in 44% of the cohort. Additional diagnoses were common. Using a cluster analysis methodology, three subgroups were identified, using three cluster features, pain, fatigue, and motor skill proficiency. The subgroups differed from each other and were clinically meaningful. They were termed Low, Medium, and High Symptom Burden, to reflect proposed care needs This could represent a more targeted care approach to help direct treatment. Fatigue and quality of life are highly corelated and poor scores were more evident in the High Symptom Burden subgroup. The High Symptom Burden subgroup also reported higher burden of symptoms. Chronic pain was endemic in this population, and present across all three subgroups, varying in severity. Mean motor skill proficiency scores were below average in the Medium and High Symptom Burden subgroups. These groups require different types of management. The more complex High Symptom Burden

subgroup is more suited to an Interdisciplinary model, to reduce severity and complications into young adulthood, whereas the Medium Symptom Burden subgroup could be managed by a Physiotherapy-led approach. The Low Symptom Burden subgroup could be managed in the clinic setting, with the provision of advice, and access to resources and education.

School attendance was reported as good, but the impact of fatigue and attention issues is an area requiring further exploration. Overall, this exploratory study identified three subgroups. The clinical characteristics of each subgroup were defined. Further validation of these subgroups is required using an independent sample. Clinical profiles identified in this study used measurements which are feasible and repeatable in the clinical and research setting. This will allow for comparison on different samples and provide guidance to clinicians assessing children and adolescents with symptomatic hypermobility. Clinical subgroups will now be further explored in Study III using a qualitative methodology.

Study II Key Findings

- Standardised, clinical assessments conducted following strict protocols are feasible in a paediatric clinical cohort presenting with significant pain and fatigue
- A detailed clinical profile of the clinical characteristics of children and adolescents with symptomatic hypermobility is presented which can be compared with future studies
- Children and adolescents with symptomatic hypermobility presented with chronic, multi-site joint pain, affecting mostly the lower limb
- Participants had worse overall fatigue than children with other chronic health conditions
- Participants were not sufficiently active, with reduced function, strength and endurance compared to age and sex normative data
- Using a cluster analysis methodology, three clinical subgroups were identified and were termed Low Symptom Burden, Medium Symptom Burden, and High Symptom Burden to reflect their proposed care needs
- Providing a more targeted care approach to the subgroups, could help to direct treatment and develop better care pathways

Chapter 5 Study III: Exploring the impact and lived experience of symptomatic hypermobility in children, adolescents, and their parents

5.1 Introduction

Joint hypermobility is a common characteristic among humans (1), and particularly in children, but little is known about the specific cause and development of symptomatic hypermobility and its impact on the lives of children, adolescents and their families (1). In order to develop an understanding of the experience of symptomatic hypermobility and the impact on family life, a sequential explanatory mixed-methods design was used (23), (22). This chapter outlines the qualitative component (Study III) of this mixed methods research (Figure 5.1) (23).

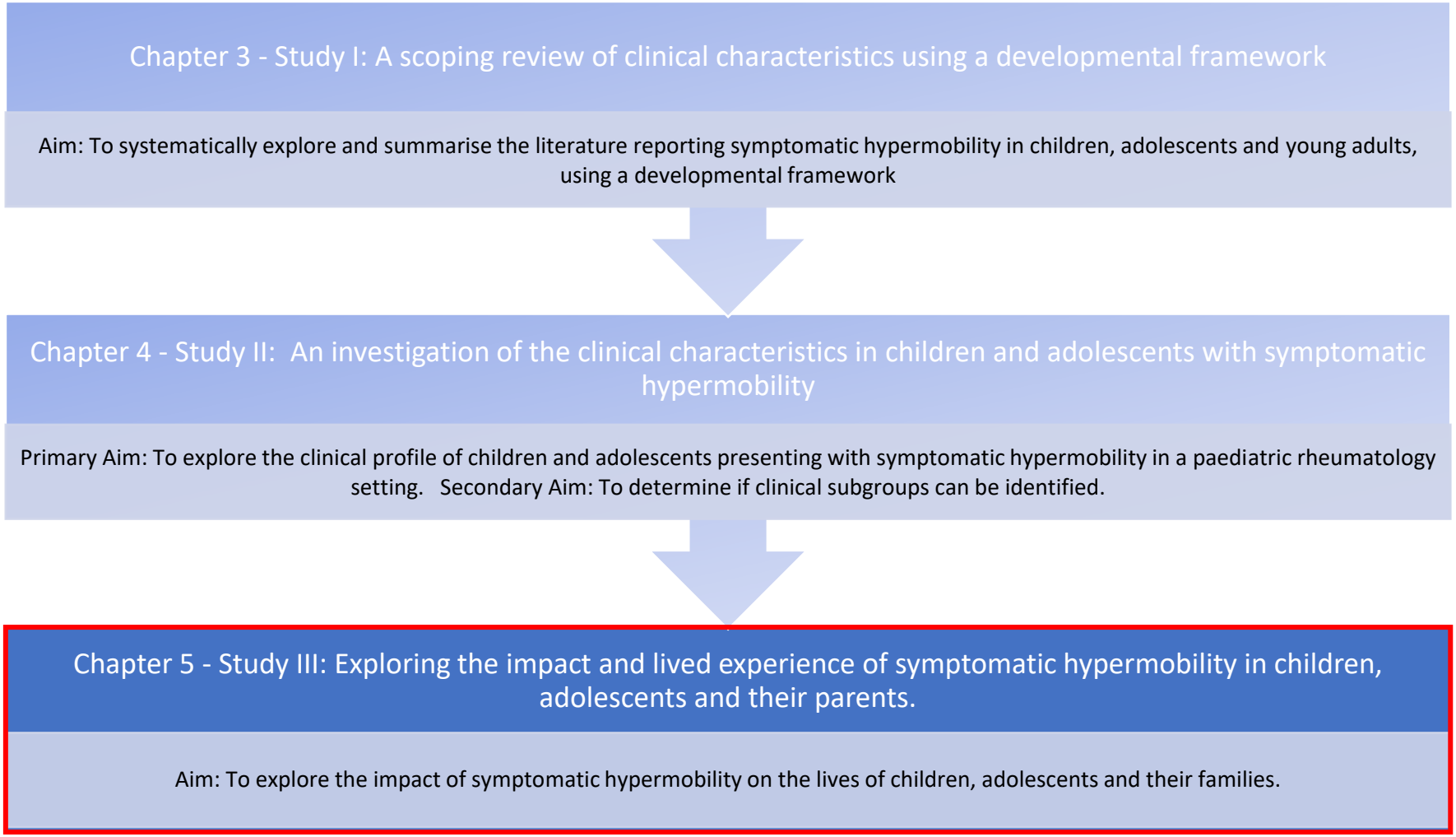


Figure 5.1 Outline of the studies in this thesis

It has been established that recognising clinically relevant hypermobility in a child or adolescent is challenging. This is partly due to methodological issues, such as the lack of standardised assessments and outcome measures, as discussed in detail in Chapter 2 of this thesis. Study I mapped the clinical characteristics in children and young people with symptomatic hypermobility reported in the literature. The review proposed that with clearer guidance for health care professionals, patients with clinically relevant hypermobility could be recognised earlier and managed locally in a timely manner, addressing the broad symptomology with appropriate support.

Study II explored clinical data from 80 children and adolescents with symptomatic hypermobility recruited from tertiary paediatric rheumatology services in Ireland. Using exploratory cluster analysis, three clinical subgroups of symptomatic hypermobility were identified. There is a movement towards the development of more targeted care pathways, as part of Ireland's waiting list action plan 2023 proposed in Ireland's 10-year HealthCare plan, Sláintecare (15, 300). Further research into the three clinical subgroups identified in Study II, could represent a movement towards more targeted treatment in this patient cohort.

Exploring the lived experience of children and adolescents with symptomatic hypermobility is lacking in the literature (188, 203, 301). Study I quantified study designs from 163 papers in children and young people with symptomatic hypermobility published from 1967 to 2021 (210), and observed that studies were mostly quantitative, with qualitative study designs accounting for only 2% (n=3) of the included studies. Tran et al., 2019 included a single open question in their study investigating symptom complaints and functioning in adolescents with hEDS using standardised questionnaires (155). Authors highlight that future interview studies are needed to better understand the impacts of symptoms (155).

Two of the studies identified in Study I, explored lived experience (188, 203), whilst the third study was predominantly a quantitative survey design, with limited qualitative data related to the experience of physiotherapy only (301). One of the first studies to explore the lived experience, view and experiences of diagnosis and management of patients (n=25) with symptomatic hypermobility (188), included data from three young adult

females (one 19 and two 21-year-olds) (188). Focus groups were conducted in non-clinical settings, using a topic guide about living with symptomatic hypermobility (188). The impact of pain, fatigue, proprioception challenges and recurring injuries were reported as challenging features of living with symptomatic hypermobility (188). Participants reported how their lives were disrupted by fluctuating symptoms and the 'cycle' of injury and recovery (188). Participants perceived that symptomatic hypermobility was poorly understood and felt stigmatised, which was later argued to have wide-ranging negative biopsychosocial consequences (188). Participants were recruited from clinical physiotherapy services, as well as patient support groups and patients with an expressed interest in research in the area, hence, whilst purposive sampling was used to aim for diversity of age, gender, socioeconomic and geographical location in the United Kingdom, this form of recruitment may have biased the sample (188). Whilst the findings are insightful, the researchers didn't acknowledge how their own backgrounds or epistemological position may have shaped the data collected. Consequently as the authors did not fully disclose this information, this may hinder the reader's interpretation of the findings, as researcher reflexivity is an important measure of quality (26, 302).

A later study, Saetre et al., 2019 sought to explore the lived experience in Norwegian adults (n=7) including three young adults (one 18 years and two 24-year-olds), using a more in-depth interview approach (203). In this study, pain and fatigue were common features in all participants, commonly described as simultaneous (203). Young adult participants also described the impact of co-ordination difficulties in functional tasks like running (203). An emerging theme was the experience of an imbalance of their bodies' tolerance and, similar to Terry et al., 2015 (188), the fluctuating nature of symptoms, irrespective of full/part time employment, disability or student status (203). Purposive sampling was used to obtain a heterogenous sample and strict inclusion criteria included a clinical diagnosis of symptomatic hypermobility (JHS/EDS-HT) and the interview guide was detailed. Furthermore, a reflexive approach was taken as the researchers disclosed their backgrounds and their epistemological stance, whilst the methods were outlined in a step-by-step basis (203). Whilst the sample size was deemed appropriate considering the in-depth nature of the interviews and the authors did attempt to obtain a

heterogenous sample participants were all newly diagnosed within 2-6 months, which needs to be taken into consideration, and moreover, as per the previous study, there were very limited findings specific to young adults (203).

The studies described above, were all included in Study I, as they fit the inclusion criteria, but participants were all young adults. There is a paucity of qualitative research in children and adolescents with symptomatic hypermobility, (303, 304), and some studies have focused purely on the parents' experience (305). These studies did not fit the inclusion criteria for Study I, but for the purposes of this study, they do offer some insight.

Birt et al., 2014 (303) used semi-structed interviews to explore how families experienced an intensive multidisciplinary team intervention (83). The study explored the family's perspective towards home exercise programmes and found that parents played an important role in adherence, and that exposure to health professionals empowered families to self-manage their condition (303). Although not the aim of the study, one parent reported the impact of not being able to walk far on their family life (303). Parent's experiences of healthcare for children with symptomatic hypermobility were also explored by Bell and Pearce., 2022 (305), who also found that awareness and understanding were fundamental, but conversely to Birt et al., 2014 (303), reported that in their study parents were frustrated by the lack of understanding by health professionals, and their frustration at having to research and 'figure it all out by themselves' (305).

A third study, Lumley et 1994., (304) examined psychosocial functioning in patients with EDS, which was also not included in the review in Study I, as it included all types of EDS. The authors report the finding that children with symptomatic hypermobility (EDS III or JHS as it was termed in their study, using previous diagnostic criteria), had greater psychosocial disturbances that other rare forms of EDS, postulating that the chronic, debilitating pain may explain this increase (304). This early paper emphasising the need for professional attention to a patient's psychosocial health, is an early reflection of the importance of a biopsychosocial approach in this population.

Similar to the research on symptomatic hypermobility, the literature in the broader area of paediatric chronic pain, which commonly includes participants with hypermobility, also consists predominantly of quantitative studies (306). Recognising this knowledge gap authors explored the lived experience of adolescents (n=7) with chronic pain and co-occurring mental health issues, which also included three adolescents with hypermobility (306). The authors described how 'Daisy', a 15-year-old with hypermobility, chronic pain, scoliosis, anxiety and depression, described her symptoms as a 'whirlwind of everything', to depict her symptom flare ups, described as 'unexpected, and seemingly random' (306). Credibility, transparency and rigour, were evident in this study which used interpretive phenomenological analysis to study seven participants in depth, rather than breadth (306). This novel study, of whom 40% of the participants had self-reported hypermobility, emphasised the need for researchers to focus not only on the impacts close to home, and highlighted the social ramifications and drivers of the challenges described by participants, and encourages future research to 'zoom out' to explore these systemic influences in society (306). The fact that diagnoses were again self-reported and medical chart records were not used to verify diagnoses, is a limitation to this study (306).

Whilst there have been no qualitative studies exploring the lived experience from the perspective of children and adolescents with clinically recognised symptomatic hypermobility, there have been qualitative studies in children and adolescents with other genetically determined Hereditary Connective Tissue Disorders (HCTDs) (307). A recent study explored adolescents' perceived impact of Marfan syndrome on functioning and disability (307). Interviews were conducted with n=19 adolescents age range 12-17 years (307). The presence of joint hypermobility is a common clinical feature and adolescents perceived limitations and restrictions in physical functioning including difficulties in keeping up with peers, however the presence of other clinical features including cardiac, facial and skeletal features, limit any comparisons (307).

5.1.1 Rationale

The current research field on paediatric hypermobility lacks insight, with limited research using qualitative methodology (188, 203, 301). Qualitative methodologies encompass an interpretive approach to data collection and analysis, focusing on the meaning people attach to their experience (302). They can also play a role in validating data collected quantitatively, to give a different perspective on the same phenomena (302). Previous research has neglected to explore symptomatic hypermobility from the perspective of the child, or adolescent, using established qualitative approaches.

A recent call to action published in the Lancet, in 2020, appealed for transformative action in paediatric pain, "to make pain matter, make pain understood, make pain visible and make pain better " (308). My personal clinical experience recognises this research gap and acknowledges this call for action. This study is the first to the authors knowledge, to focus on the impact of clinically determined symptomatic hypermobility from the perspectives of children, adolescents, and their parents.

New knowledge may be provided, which may assist health care professionals in better understanding the experience of symptoms on patient's lives, as well as setting meaningful goals for the patient and their family. This may help researchers and clinicians better comprehend the lived experience of children and adolescents with symptomatic hypermobility.

5.2 Research question

What is the lived experience and the impact of symptomatic hypermobility on the lives of children, adolescents, and their families?

5.2.1 Overall study aim

To explore the lived experience, and the impact of symptomatic hypermobility on the lives and family functioning of children, adolescents, and their families.

5.2.2 Objectives

1. To improve our understanding of the impacts of symptomatic hypermobility on children, adolescents and their families i) at home ii) at school iii) during activities and iv) with their peers.
2. To explore if reported symptoms changed over time, as perceived by children, adolescents and parents.
3. To explore the impact of Covid-19 on families lives in respect to symptomatic hypermobility.

5.3 Methods

A descriptive qualitative study design, using semi-structured interviews was chosen to address this research question (309). In qualitative descriptive studies, data collection attempts to discover "the who, what and where of events" or experiences (310). This type of approach allowed for the presentation of the depth of information described in this qualitative study (310). This approach was suitable as it also fit other features of the study including the choice of pragmatism as a paradigm for the study, the use of a purposive sampling technique (in this case maximum variation), the use of semi-structured interviews, the use of thematic analysis and the provision of a descriptive summary of the data which was presented in a way that best fits the data to describe the lived experience of the child, adolescent, and parent participants.

This qualitative study was used to complement previous studies in this PhD, bringing together knowledge gained from both the scoping review and the cross-sectional study, used to develop the research aims, and subsequently, informed the development of the interview guide and the sampling technique which was used in this study. This qualitative research also plays a role in validating the previous quantitative study, providing a different perspective on the same subject, studied quantitatively (302).

5.3.1 Semi-structured interview

An interview approach using a semi-structured interview is the most widely used format for qualitative research (311). A structured interview, often using closed questions, isn't intended to generate qualitative data (302). At the other end of the interview spectrum the individual in-depth interview, often focuses on only a few, open questions, allowing for the participant to reflect and speak at length (302). Semi-structured interviews were deemed most appropriate in this study as they are based on a set of predetermined open-ended questions, with the option for further topics emerging during the interview process (311). Semi-structured interviews are a common method used to seek a deeper understanding of human experience [179]. This method was suitable to both the research aims, and the participant age groups which involved young children from the age of 6 upwards.

5.3.1.1 Online interviews

Originally, it was intended that interviews would be conducted in person. However, in response to the social distancing policies enforced due to the Covid-19 pandemic during this time, the decision was made to conduct interviews using a secure online platform (312). Moving to an online approach was not a straightforward transition and a number of factors were taken into consideration (313).

Firstly, ethical issues such as privacy concerns were considered. The secure management of the collected data, including recording, storage and consent was also reviewed following the change to an online approach. These issues are described in further detail in the Data Protection Impact Assessments (Appendix 10 & 11).

Secondly, the concern of potentially excluding families due to their lack of technological resources was considered. This concern was significantly reduced due to the widespread transition to online communication during the Covid-19 pandemic. Families across Ireland had become familiar and proficient in using technology for work, education and socialising. Transitioning from in person, to online data collection had a benefit in that it also broadened access to families from both rural and urban areas all over Ireland, reducing the burdens of cost and time, to travel to the research location (313).

Thirdly, adapting to potential technological challenges. Before data collection commenced, participants were informed of the type of online platform which would be used, the access to hardware (phone or tablet or PC with reliable internet access), and support options to respond to possible problems. To facilitate social interactions and establishing rapport, cameras were used at all times.

Fourthly, clear strategies to respond to a child or parent who may become distressed in the online setting was set out in the patient information leaflet (Appendix 15) as detailed in the revised ethics application (Appendix 7 & 9). Written consent and assent were given prior to any data collection, and verbal continuous consent was requested at the commencement of each interview (314).

5.3.2 Pragmatic approach

A pragmatic approach was used for this study (315). In comparison to other metaphysical paradigms, pragmatism takes the view that researchers choose which questions are important to study, and which methods are most appropriate to answer those questions (315). Rather than taking a specific philosophical stance, the pragmatic approach takes a 'real world' approach where the researcher can move back and forth between the knowledge gained from quantitative and qualitative research, 'to search for useful points of connection' (315). This approach redirects attention to how we use methods, rather than specific research methodology, and builds on how the researchers' world views, influence their research, continuing a reflexive outlook towards research. Using this approach conceptualises the researcher as a resource for knowledge, rather than a threat to credibility (316).

5.3.3 Sampling and selection criteria

A sub-sample of children and adolescents recruited in Study II were selected for interviews in Study III. A purposive sampling method was agreed by the research team, and aimed for maximum variation, to include the desired diversity of the sample, including heterogenous cases, to capture the differences, similarities, critical cases,

typical cases, and deviant (outlier) cases (302, 317, 318). Variation included biological sex, age, geographic location to include variation of rural and urban locations, and symptomatic hypermobility severity. Two age groups were used for sampling: 6 to 9 years and 10-16 years, to correspond with the same defined age categories used in Study I and Study II. Currently, there are no measures to determine symptom severity in paediatric hypermobility. Based on the earlier subgrouping analysis in Study II, purposive sampling was aimed at capturing differences across the cases presenting with variations in symptoms, found in the three identified subgroups (Low, Medium and High Symptom Burden).

Inclusion criteria

Children and adolescents were included if they were between the age of 6 and 16 years, recognised as having symptomatic hypermobility, determined in the paediatric rheumatology clinic setting in a tertiary children's hospital. Secondly, an ability to communicate in English with an interpreter, if necessary was required. Thirdly, participants had previously participated in Study II. Lastly, children, adolescents and their parents/guardians had to be able and willing to give continuous, verbal consent (Table 5.1).

Exclusion criteria

As participants had already participated in Study II, the following exclusion criteria which were used in Study II were used again: a diagnosis of inflammatory disease, trauma or surgery unrelated to symptomatic hypermobility that would affect functioning and any other significant co-morbidities that would affect the ability to participate in the objective testing (Table 5.1).

Table 5.1 Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Aged between 6 & 16 years and Recognised as having symptomatic hypermobility	Diagnosis of inflammatory disease, trauma or surgery unrelated to symptomatic hypermobility that would affect functioning and any other significant co-morbidities that would affect the ability to participate in the objective testing
Ability to communicate in English	
Previously participated in Study II	
Children and Parents / Guardians able and willing to give consent	

5.3.4 Sample Size

The final sample size was decided in-situ and was shaped by a number of factors. Initially, previous literature in similar cohorts using a qualitative approach were used to guide the initial sample size (307, 319). Qualitative researchers are now called to explain how samples are adequate, appropriate and aligned (320), therefore, the focus was shifted towards the quality of data collected, rather than the quantity alone (318). The sample required to answer the research question was the greatest influence in this study, using a concept called information power (321). This concept indicates that the more information the sample holds, the lower the amount of study participants is needed (321). Sufficient information power is also determined by i) the aim of the study, ii) sample specificity, iii) use of established theory, iv) quality of dialogue and lastly, v) analysis strategy (321). This concept is not tied to any specific theory or theoretical sampling, which was in keeping with the pragmatic approach used in this study (315, 321). The children, adolescents and their parents/guardians were a subsection of participants who were recruited and participated in Study II. Other factors such as the exploratory nature of the study, the quality of dialogue, the consideration of the demands placed on participants, and analytical goals, were also taken into consideration when considering the sample size (318, 321).

5.3.5 Participant recruitment

Following purposive sampling, parents were contacted by email to enquire if they and their children were still willing to participate in the qualitative study. Parents and children were already aware that they may be invited to take part in the interview study, from the overall PIL (Appendix 15). Once parents expressed interest regarding participation in the study, an introductory email was sent to participants, outlining the procedure that would be followed. Any questions regarding hardware, or software, privacy concerns, and issues regarding data management were re-iterated at this point. Data collection ended after 18 interviews with children and adolescents and 22 interviews with parents. This was an interpretive judgement which related to the aims of the study and the purpose of the analysis, following discussion and agreement with the wider research team (318).

5.3.6 Reflexivity

It is widely accepted that data from the interview process is socially construed because of the interaction between the interviewer and the participant (302). The researcher's own views are recognised as part of the interview process, whereby the researcher plays an active part, shaping each stage of the process (320). Ensuring that the process of analysis was transparent, with clear reporting and involvement of the wider research team, was crucial to the reflexive process (320).

As a clinician, with over 20 years' experience working with children and their families with symptomatic hypermobility, it was important to consider how this would shape my interpretation of the data. As a novice qualitative researcher, I completed significant training in qualitative methods in healthcare, including over 30 hours of instruction, which included thematic analysis and theoretical methodology. I was also aware of my own role as a parent of three school-aged children. Additionally, I reflected on my position relative to the participants. As a researcher, I had met each participant in an earlier study, but I was not involved in their clinical care at any stage. I ensured that during the online interviews, I wore non-clinical clothing, to reinforce my role as researcher, rather than clinician. Using 'lay' rather than medical language was important during the interviews, to avoid using terms that families would not be aware of (302).

Likewise, asking participants to explain the meaning of a particular phrase was important, especially considering social or cultural inferences, specific to each family (302). Building rapport at the start of the interview was used to help to put the child or parent participant at ease, as well as using active listening and eye contact, with cameras of both researcher and interviewee turned on. As reflexivity is a continual process, a reflective diary was kept (Figure 5.2) and regular team meetings with my supervisor and wider supervisory team were held, for reflexive discussion (322).

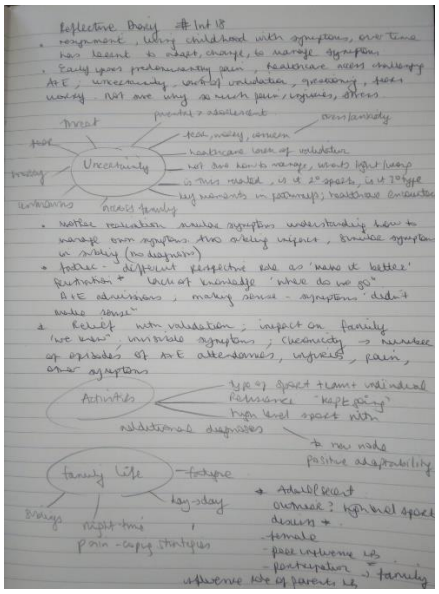


Figure 5.2 Reflexive diary example

5.3.7 Reflexive thematic analysis

Reflexive thematic analysis was used in this study (316). It is a flexible, iterative and analytical process, useful for exploratory studies and helps to identify relationships between themes (309). A predominantly inductive thematic analysis was used in this study, which means that largely, the data itself shapes the themes (309), whilst being aware of the research aims and also the researcher's own role in data collection. Thematic analysis is not bound to a specific theoretical framework, therefore can be used within a pragmatic 'real world' approach, to reflect reality but also to unpick the surface of 'reality' (309). These themes can develop during the analysis process, whilst considering how the researcher's beliefs, values and subjective perceptions may shape

the analysis (302, 309, 320). The analytical process requires immersion in the data, in a process including reflecting, reviewing, questioning, imagining and returning to the data (316).

5.4 Ethics considerations

Ethics approval was gained from Trinity College Dublin and Children' Health Ireland Research Ethics Committees (Appendix 7 & 9). This study was reported according to the Consolidated Criteria for Reporting Qualitative Research (COREQ) Guidelines (Appendix 29) (26). The sample was described to allow the results to be representative of other similar cohorts, without compromising anonymity (302). Verbatim text from the interviews that contained identifiable data such as names or places, was replaced with a general term, and framed with square brackets.

E.g.," [The consultant haematologist] just said, Oh, let me just ask physio to come over, just one second".

Written consent and assent were given prior to any data collection, and verbal continuous consent was requested at the commencement of each interview (314).

The Covid-19 pandemic affected all of society as governments adopted public health policies to attempt to reduce the spread of the virus (COVID-19 (coronavirus) - HSE.ie). As this study was carried out shortly after the period of widespread school, sporting and health facility closures, ethics amendments to conduct online interviews rather than in person were applied for and granted (Appendix 7 & 9). The video conferencing platform Zoom was chosen, as it was acceptable by the Research Ethics Committees, and has been reported as intuitive and user-friendly (221, 312, 323).

There were challenges which needed to be addressed (313). Participants were encouraged to engage online with their camera on and although this introduced a risk to the participants privacy, all participants were made aware of this before the interview commenced. Families were encouraged to find a quiet space where they would not be disturbed if this was possible. A distress strategy to respond to a child or parent who may

be upset, was detailed in the ethics application and in the Participant Information Leaflet. As participants were all current patients under the care of a tertiary children's hospital, the safeguarding policy protocol according to Children's First (324) was the designated protocol for any child or parent in distress.

5.5 Data management

A data management impact assessment (DPIA) was conducted to detail the procedures that would be followed regarding the data collection process, recording of data, secure storage of data, and when and how recordings would be deleted, and data would be destroyed (Appendix 10 & 11). Participants were purposively sampled from the previous observational Study II. Data from Study II were pseudonymised using a study identification number recorded on a patient master identification list, and this was used to identify participants for Study III. Once data had been collected for the current study, and member checking had been completed, all identifying details were anonymised, the recordings were deleted from all hardware, and only anonymised transcripts remained. Transcriptions were stored on an encrypted, password-protected computer. Full details of data management including data type, access and storage can be found in Appendix 10 & 11.

5.6 The interview guide

The interview schedule was designed to enquire about impact of symptomatic hypermobility on different aspects of children, adolescents and their families' lives. The interview schedule focused on the research question, the researchers' knowledge of the field, and the relevant literature. The schedule was designed in three parts (Table 5.2), in order to allow for rapport building, and to generate rich data, while not being too onerous for the child, adolescent or parent. Building rapport was an essential part of the process to help the interviewees feel at ease (302).

The first part of the interview was the introduction. This included simple explanatory materials and consent, the aims of the research were explained, participants were

reminded that each interview was being recorded and assured of their anonymity, and participants were given an opportunity to voice any questions. Following this brief introduction, the first two questions were asked (Table 5.2).

The second part of the interview explored the core phenomenon, the impact of symptomatic hypermobility on different aspects of a child, adolescent, or family's life. This was the heart of the interview. The researcher also probed participants to discuss topics further, such as 'Can you tell me more about this?' following the interview guide questions (Table 5.2). The interview guide was followed but was flexible, and not prescriptive, to allow adaptation for younger children for example. This approach also allowed for any new aspects or experiences to emerge over time (302).

The third part was final reflections. This allowed for an open question, which gave an opportunity for any comment the interviewee might care to make, that had not been previously covered during the interview.

Table 5.2 Interview guide for semi-structured interviews

Guide for Parents/Guardians Interviews
PART 1
Can you tell me about your child/teen's symptoms? Can you tell me about what symptoms bother your child/teen the most?
PART 2
What is the impact of your child/teen's symptomatic hypermobility on siblings, partner or extended family? What is the impact of your child/teen's symptomatic hypermobility on your work/occupation? What is the impact of your child/teen's symptomatic hypermobility on family activities/outings? Can you tell me about how/if having symptomatic hypermobility has an impact on your child's life? Has the impact of your child/teen's symptoms changed from childhood to adolescence?

In your opinion, how did Covid-19 affect your child/teenager?
PART 3
Close Is there anything else that you think is relevant that you would like to tell me about?
Guide for Child/Teen Interviews
PART 1
Can you tell me what symptoms you have? Can you tell me what symptom/s bothers you the most?
PART 2
Does having hypermobility affect your life? a. at home b. at school c. during activities d. with your friends Has the impact of having hypermobility changed from when you were younger, compared to now? During Covid-19, there were lots of changes to our lives. Did these changes affect your symptoms?
PART 3
Close Is there anything else that you think is relevant that you would like to tell me about?

5.7 Pilot study

Prior to conducting the study, interviews were conducted with two families not included in the study who matched the inclusion criteria. This allowed the researcher to explore the suitability of the interview guide with parents and children. During these interviews, regular feedback was provided by the families involved. Following this process, the introduction was streamlined to ensure that correct procedure was followed and that the research aims were clear. No changes were made to the interview guide question topics.

However, it was noted by both families, that changing the language, depending on the age of the child, would be necessary and should aim to be simplified wherever possible.

5.8 Data collection

Online interviews took place between April and October 2023. Where possible, children and adolescents were interviewed separate to their parents. A modified interview guide was used, and the wording was adapted where necessary according to the age and developmental stage of the child (Table 5.2). The interviews were conducted at a time that was at the convenience of the interviewee(s). Each interview was recorded using Zoom software (312, 323), using a setting for automatic recoding, and participants were reminded that the content would be recorded, at the start of each interview. Participants were also reminded that their anonymity was assured and that each interview transcript would be sent to them, for member checking, prior to analysis.

Most participants were at home during their online interviews. One interview took place at the parent participant's workplace during a lunch break. Another parent participant used their mobile device so that they could attend to younger children and move about their house, whilst conducting the interview. In this case, the parent quickly found a quieter space to continue the interview but was able to supervise younger children in a nearby space. This allowed families to take part in research and continue their daily lives with minimum inconvenience and cost, one of the advantages of the move to online interviews (313). Interviews were audio recorded and transcribed verbatim. The interviews were transcribed in full by the Principal Investigator. Following transcription, they were member checked by participants and the recordings were deleted. Transcriptions were stored on an encrypted, password-protected computer following the procedures as detailed in the data management plan (Appendix 10 & 11).

5.8.1 Rigour

In order to ensure that the process was trustworthy, the following steps were taken. Credibility was ensured by using peer debriefing during thematic analysis and adopting researcher reflexivity (325). Initial coding was conducted by two researchers (Principal Investigator and main supervisor) for the first three interviews, then completed by the Principal Investigator. As participants were recruited from Study II, the triangulation of quantitative and qualitative data provided a richness of data, to provide a more complex understanding of the impact of symptomatic hypermobility. The sample was described in sufficient detail so that data can be representative and therefore the transferability of the collected data will be ensured. A detailed description of the methods, data collection, type of analysis, and interpretation ensures a reliable account of the data. Confirmability was ensured by the researcher by regular consultation with the researcher team which included researchers with different backgrounds, including those with extensive experience in qualitative design. The use of an iterative process also ensured confirmability (325). Finally, rigour was enhanced by stating an awareness of the role of the researcher as an active part of the research process (302).

5.9 Results

A total of n=22 children (n=8) and adolescents (n=14) were included in the study and a total of n=22 parents including mothers (n=18) and fathers (n=4). Two adolescents (n=2) declined to take part due to end of year school examinations in June 2023. Two children (n=2) did not participate in the interview with their mothers as they were absent (at school, and at a sporting event) during the time of the interviews. There were no parental dropouts, with 100% of invited parents taking part in the interviews. A total of n=18 children (n=6) and adolescents (n=12), and n=22 parents including mothers (n=18) and fathers (n=4) took part of in the interviews. The mean age of child and adolescent participants was 11.55 (3.5) years and 55.5% (n=10/18) were female. Two participants (n=2) were interviewed with their parents at their request, but all other children and adolescents were interviewed separately from their parents. When both parents were interviewed (n=4 families), mothers and fathers were together during the interviews.

The online interviews took place between April 2023 and October 2023, in a private office space at a time convenient to both parties. Interviews ranged in time from 30 minutes to 68 minutes in duration (mean time 45 minutes). There was one minor technical difficulty experienced with a poor signal, but this was temporary, and the signal was re-established quickly. Immediately after the interviews, reflective notes were made. Based on the subgrouping analysis in Study II, n=3 (17%) were in the Low Symptom Burden subgroup (*Low*), n= 11 (61%) were in the Medium Symptom Burden subgroup (*Medium*) and n=4 (22%) were in the High Symptom Burden subgroup (*High*). Child and adolescent participant demographics and clinical characteristics are presented in Table 5.3. Demographics were not collected for parents as this was not included in the overall aims of this study. All names, places and identifying information has been replaced by generic terms, contained within square brackets. Participants have been described by their age in years, their biological sex and subgroup allocation in Study II (Low, Medium, or High), to ensure anonymity and confidentiality. In this study, themes are supported by direct quotations. The [ ] symbol refers to added information by the author for explanation or comprehension.

This study was reported according to the Consolidated Criteria for Reporting Qualitative Research (COREQ) Guidelines (Appendix 29).

Table 5.3 Clinical characteristics of child and adolescent participants

Participant	Gender	Participant age (years)	Clinical Subgroup ¥	Pain Scores [a]	BOT-2B percentile [b]	Fatigue Scores [c]	Other diagnoses [d]
1	Female[s1]	6	Low	0.5	95	78.00	DDH
2	Male	13	Low	3	90	75.00	SPD
3	Male	15	Low	8	97	100.00	Nil
4	Female[s2]	10	Medium	4	31	68.06	DCD, POTS
5	Female[s2]	13	Medium	5	24	64.44	Coeliac, Allergies, MCAS, Chronic Pain, Anxiety, DCD, POTS
6	Female	9	Medium	5	21	69.44	Primary Raynaud's, SPD
7	Male[s3]	13	Medium	7	21	52.90	Psoriasis, IBS, Anxiety
8	Male[s3]	11	Medium	4	27	57.00	GOR, Constipation, Allergies
9	Male	8	Medium	1	24	86.20	Pes Planus
10	Female	8	Medium	0.5	24	41.70	Eczema, Constipation, Blepharitis
11	Male	10	Medium	2	35	86.20	DCD, ASD, Speech Delay
12	Male	16	Medium	5	38	79.17	Scoliosis, Asthma
13	Female	15	Medium	4.5	1	41.67	Chronic Pain, Anxiety, POTS, Migraine, DCD
14	Female[s1]	13	Medium	2.5	54	22.30	POTS, Chronic gastritis, Fatigue, Chronic Pain

15	Female	6	High	9	16	42.00	GOR, Constipation, Infant Talipes and Torticollis, Headaches, Speech Delay
16	Male	9	High	10	29	18.06	Speech delay, Dyslexia, Allergies, DDH, Scoliosis, GOR
17	Female	17	High	8.5	21	25.00	Scoliosis, Primary Raynaud's, Migraine
18	Female	16	High	6.5	27	23.70	Dyslexia, DCD, Allergies, Asthma

[¥] Clinical subgroup as reported in Study II, [a] VAS Visual Analogue Scale 0-10 where higher indicates more pain, [b] Bruininks-Oseretsky Test of Motor Proficiency- Brief Version percentile rank compared to standardised normative data, [c] MFI Multidimensional Fatigue Questionnaire Scale 0-100 where higher indicates less fatigue, [d] Reported diagnoses during structured interview Study II, [s1,2,3] Sibling Groups. DDH Developmental Dysplasia Hip; SPD Sensory Processing Disorder; DCD Developmental Co-ordination Disorder; POTS Postural Tachycardia Syndrome; MCAS Mast Cell Activation Syndrome; IBS Irritable Bowel Syndrome; GOR Gastro-oesophageal reflux; ASD Autistic Spectrum Disorder.

5.10 Data analysis

Thematic analysis was conducted in a 6-step process as described in the original text by Braun and Clarke, 2006 (309). Each step is described in detail below:

Step 1:

Familiarising yourself with the data (309). As only one researcher was involved in the data collection process, the data were already familiar. Regardless, this stage involved repeated reading of the data, and listening to the audio-recorded interviews in an active way searching for links, meanings and patterns (309). All interviews were recorded and transcribed as a verbatim account by the Principal Investigator using Zoom video conferencing software (312). Software dictated the audio transcript for each recording onto a Microsoft Word transcript. Each transcript was reviewed and checked for accuracy, especially with regard to punctuation or mannerisms. Once transcripts were written, they were cross-checked back against the original audio for accuracy (309). At this stage, transcripts were sent back to the participants for member checking (302). Two participants responded following this step. The first respondent added some extra text to include information they felt was relevant to the interview, which they had left out. The second respondent clarified some of the language used in the interview. In both cases, this resulted in additional original data. This extra data provided further insights and was used to help to inform the researchers understanding of the collected data (320). Involvement of the participants via member checking was also important to introduce a sense of partnership between the researcher and participants, enriching the data collection process (320). After the member checking process, the data were anonymised and the transcribed, interview data were uploaded onto NVivo V1.6 software (326)

Step 2:

Generating initial codes (309). Transcribed, anonymised interview data were uploaded onto NVivo V1.6 software (326). Each line of each interview was systematically reviewed, and 'nodes' (NVivo codes) were named referring to distinct quotes which were informative, or interesting and relating to the research aims (Table 5.4). These nodes

captured usually just one entity; however, the context of the subject was also kept if relevant. This was repeated for each interview.

Table 5.4 Data extract with nodes applied

Data Extract	**Node**
…like my symptoms kind of change up, like one day, my hips will be really bad. And then the next week, it'll be something else completely different. So it's like really hard to gauge. Like when I go to physio, it would be like once every couple of weeks. So a new problem would crop up. (Participant 17, 17-year-old female, High subgroup)	1. Fluctuating symptoms 2. Challenges to management

Nodes created in NVivo, were subsequently explored (Figure 5.3) using NVivo 'Explore Diagram' (326), to identify similarities and differences between transcript nodes.

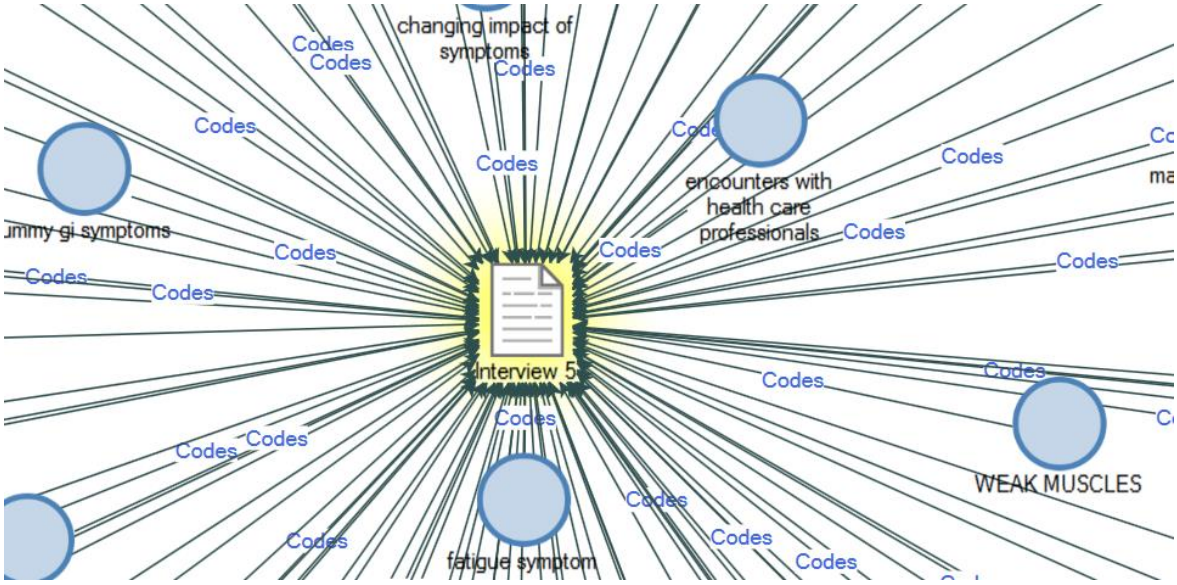


Figure 5.3 Example of early exploration of nodes, codes and potential themes in a transcript using NVivo 'Explore Diagram'

Step 3:

Searching for themes (309), was carried out by the Principal Investigator and all members of the thesis supervisory team. As well as this, consultation was sought with a researcher experienced in qualitative research to further develop the search for themes. Nodes were sorted into potential themes using multiple mapping techniques. At this stage, early links, meanings and patterns were identified, in a non-linear stage involving moving backwards and forwards from the transcripts to the emerging interpretation. Mind mapping was used to assist this process (Figure 5.4) (302).

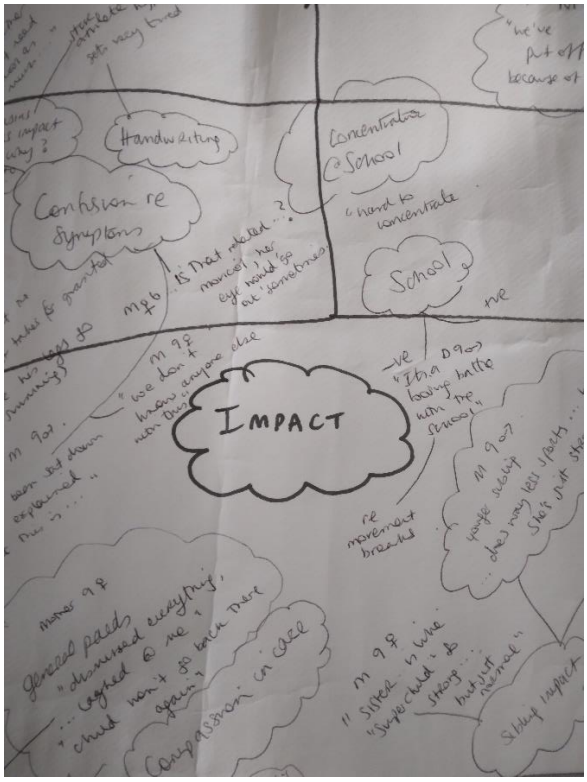


Figure 5.4 Early links, meanings and patterns using mind mapping.

The provisional themes were considered whether they were one or multidimensional, drawing together patterns across the data (316). Reflections were made in a reflective diary during this process. This process was conducted by two researchers for the first three interviews, then completed by one researcher. This was to help researchers engage in peer reflection, understanding their active involvement in the process of interpreting nodes (320).

Step 4:

Reviewing themes. (309). Following this stage, the nodes were categorised, and subsequently sorted into potential codes and emerging themes, suggesting concepts which addressed the objectives of the study (327). Following this, emergent themes were configured into theme piles (Figure 5.5) (326). Reviewing these themes was conducted by the Principal Investigator with consultation firstly with one member of this thesis supervisory team followed by broad consultation with the full thesis supervisory team. This stage involved reviewing and refining themes, which is described as a creative and active process (316). All the collated extracts were re-read, and the consideration of patterns, such as similarities or differences, were reviewed. Relationships between themes were also considered. This revision occurred until no further revisions were adding anything substantial to the overall meaning of the analysis. Each theme was reviewed, refined and renamed until the final thematic map was decided upon (Figure 5.6) (309).

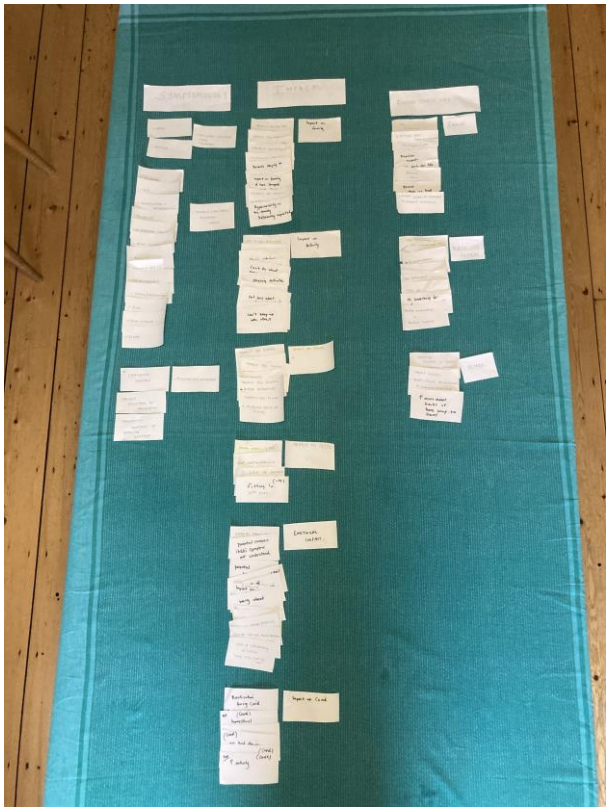


Figure 5.5 Theme piles potential theme development

Step 5:

Defining and naming themes (309). Once the final thematic map was decided upon, the data within each theme were defined, and refined in order to understand the construction of the theme (320). This involved collating the themes by going back to the data and ensuring that the accounts were consistent and made sense. Each theme was described identifying the interesting points and backed up with narrative quotes (309). The relationship of the themes to each other, and to the overall research aims was also detailed. Overarching themes were described, and within each main theme, subthemes were detailed. Names for each theme were applied. Defining and naming themes was conducted by the Principal Investigator and broad consultation with the full thesis supervisory team.

Step 6:

Reporting phase. This involved the write up of the analysis. Extracts were embedded in the text, illustrating the subtheme, or the overall theme.

5.11 Themes and subthemes

Three overall themes were constructed: 1) The need to make sense of symptoms, 2) Symptoms shape lives 3) Care pathway challenges (Table 5.5).

Table 5.5 Main themes and subthemes

Themes	**Subthemes**
1. *The need to make sense of symptoms*	Uncertainty of symptoms
	Fluctuating symptoms
	Threat, fear and worry about symptoms
2. *Symptoms shape lives*	Impact on family life
	Impact on schooling
	Impact on peers and activities
	Impact of Covid-19
3. *Care pathway challenges*	Access to resources
	The search for management of symptoms

The final main themes are shown in Table 5.5. The thematic map represents a more detailed summary of the potential connections and links between the three themes and subthemes (Figure 5.6). Arrows link themes and subthemes, in certain directions, or multidirectional if connections could be interpreted in both directions, which was often the case. The overall interpretation of the data was that the lived experience of symptomatic hypermobility impacts many facets of family life. Symptoms are complex, chronic in nature and fluctuate.

Parents, children, and adolescents discussed the nature of symptoms. Parents and adolescents expressed their uncertainty with regards symptoms. Parents were found to express a feeling of threat, worry or fear, of the future, about services, and about the development of symptoms. Impacts at home were significant, affecting everyday family activities. The significant changes to lives during the pandemic were a spotlight on issues for some, whilst others found symptoms improved with the freedoms that came with less structured schooling. Even though the topic of the interview was the impact of symptoms, parents were often focused on management, reporting how their engagement with pathways of care had impacted symptoms. Pathways to care were often reported as complicated, with descriptions of challenging health care encounters,

or difficulty implementing recommendations for schools or amongst peers. Some families had faced challenges, and found solutions, which were working positively for their child and wanted to share their journey, to help others navigate their way.

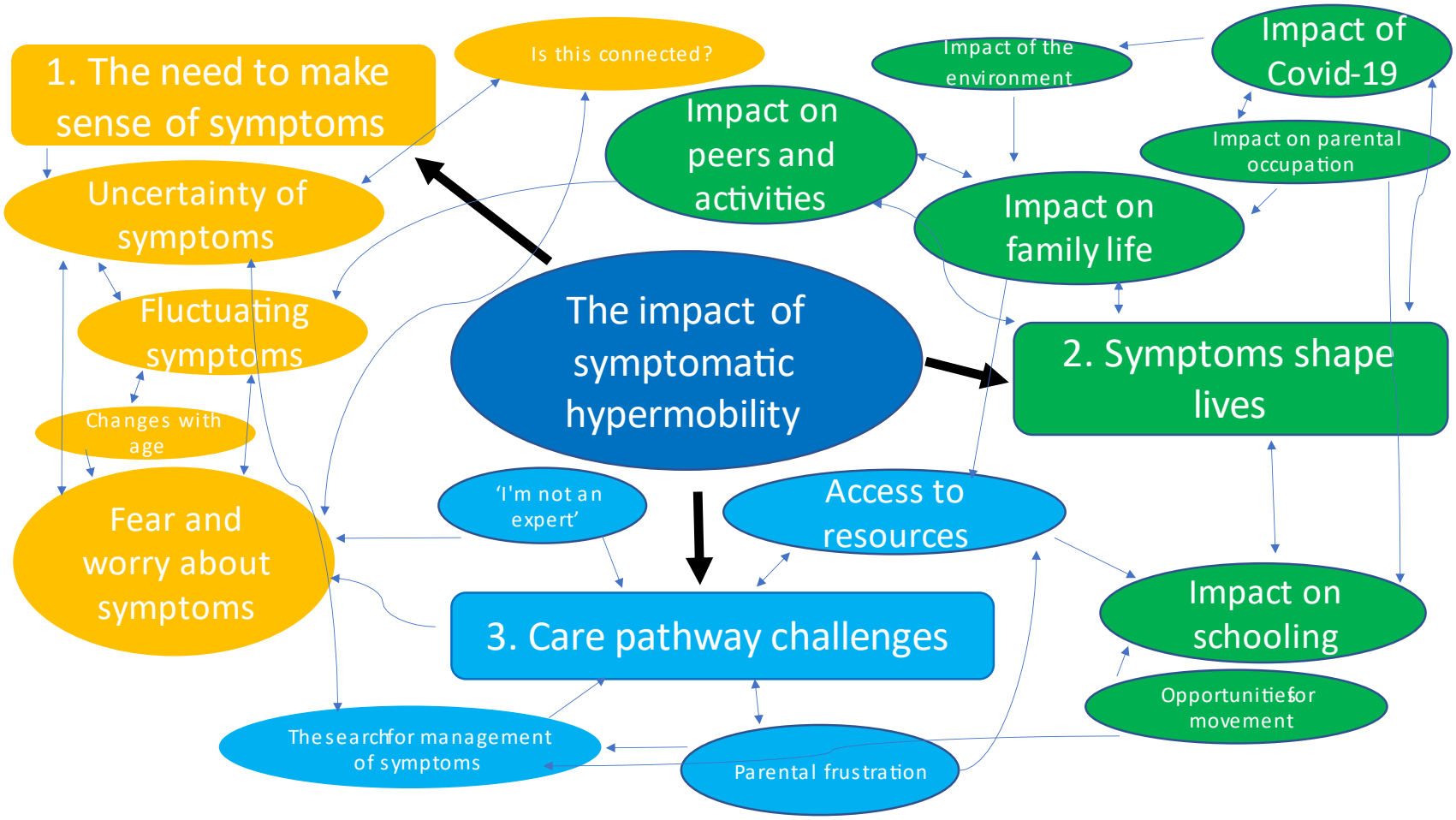


Figure 5.6 Final thematic map overview of the three themes, how they relate and link or connect with each other

5.11.1 Theme 1: The need to make sense of symptoms

"...I want to know what's going on.."

5.11.1.1 Uncertainty of symptoms

Parents, children, and adolescents unanimously agreed that fatigue and pain were the symptoms which impacted them most. Fatigue and pain appeared to be more easily understood by participants, who tried to provide some insight as to the why, but varying levels of uncertainty were present as is evident in the quotes below:

"I do get pains in my legs and my arms sometimes…. my legs get tired sometimes…" (Participant 6, 9-year-old female, Medium Symptom Burden subgroup)

"A big one is tiredness for sure. Um, I find that I get much more tired, much more quickly, and it takes longer for me, uh, to kind of repair or recover after, um, like doing a long bit of exercise, let's say, um, than it would like others in my class " (Participant 8, 11-year-old male, Medium Symptom Burden subgroup).

"I just tell them I get tired-er, more quickly. Uh, cause I, don't know the nuances of it.'" (Participant 7, 13-year-old male, Medium Symptom Burden subgroup).

One father describes how his daughter, a keen athlete, who has always enjoyed sports, has experienced pain since a young child and now experiences increasing numbers of injuries and questions why:

"she used to wake with pain. Every night…especially with the Irish dancing, she'd get pains after it, she'd wake up, so we'd have to give her like, paracetamol or Nurofen or something, or rub her legs, and as she's got older, well it's just the injuries as well, isn't it, or we don't know if that's because she's bendy or whether it's just unfortunate..." (Father, participant 18, 16-year-old female, High Symptom Burden subgroup)

Pain was often in more than one location and harder to pinpoint, as demonstrated by both an adolescent and a parent below:

"…usually it's in my knees or my ankles or my, just like the legs in general, but it's typically around the knees or the ankles." (Participant 12, 16-year-old male, Medium Symptom Burden subgroup)

"I would've said her neck, but that's just, maybe that's the one she complains of the most. Maybe she's more used to, and the legs can take it more. I would, I would've said the hips before… at the moment, now I'm saying the neck…that's what I would see bothering her more. That's the one she has to hold. That's the one that bothers her when you're doing simple tasks like her hair. Yeah, she kind of pushes through the others. You know, her hips used to bother her, but I haven't heard her complain about them much now lately." (Mother, participant 1, 6-year-old female, Low Symptom Burden subgroup)

Symptoms beyond pain and fatigue were harder to comprehend as parents wonder, and question, trying to get a sense of what's going on, reflecting, and considering options as they talk, considering connections or links, based on what they might have read, or heard. Parents are searching for answers, and often finish statements with questions:

"she gets a lot of stomach pain as well, I dunno if that's having to do with it all…the headaches, I dunno if they're having to do with it either, but they, she complains a lot of pain, you know…would the hypermobility cause the headaches and all this pain that she has, do you think?" (Mother, participant 13, 15-year-old female, Medium Symptom Burden subgroup)

"...when he is exercising, he can feel faint, or he gets fast palpitations, or he can pass out and drop. Now, when he was smaller, they said they were silent seizures. But they continued and now they're not calling them silent seizures, they're just saying, 'oh, he's getting dizzy, it's his blood pressure. I wholehearted think the hypermobility and the

cardio are connected …I do think there's something, I think they're just a bit weaker and from reading up on it, they say, your insides can be a bit weaker…now, I don't know if it is a hundred percent connected. I won't be surprised if when we see cardio that they do link the two together…" (Mother, participant 12, 16-year-old male, Medium Symptom Burden subgroup).

"Cramps and, um, like the slow emptying of her bowel…she would've had haemorrhoids like then, like, okay, one haemorrhoid that stayed for years and I didn't understand, she would've been like constipated as a toddler...yeah, constipation was always her thing, you know? I put back then she was a reflux baby…I put down to a lot of her stomach issues being all because of reflux. But actually we're, at this age, I'm thinking that that's actually not, it's, yeah. you know, maybe the reflux was related back then. I don't know." (Mother, participant 6, 9-year-old female, Medium Symptom Burden subgroup).

Whilst not fully understanding or comprehending 'why' symptoms may be occurring, the issue of diagnostic labelling was discussed by one mother of an older teenager, who explained the impact of not having a particular diagnostic term to use, as she explained how it might help her better understand what was happening to her teenager:

"I don't want to label my child, but I want to know what's going on" (Mother, participant 17, 17-year-old female, High Symptom Burden subgroup)

5.11.1.2 Fluctuating symptoms

Symptoms were described as changing and fluctuating by adolescents and parents, across all subgroups. Parents and adolescents had mixed perspectives on the changes with growth, with some recalling how things had improved, and others describing a worsening picture, with symptoms become more widespread and affecting different body systems:

“I get very tired and sometimes just, sometimes I get pain...” (Participant 6, 9-year-old female, Medium Symptom Burden subgroup)

“it happens anytime... it happens a lot....” (Participant 1, 6-year-old female, Low Symptom Burden subgroup)

“she used to be tired, like when she was younger. She would get tired, say if we're out for walks or things like that…but yeah, she would've, she'd love sitting in and relaxing and a busy day is probably too long or too busy on her, but recently ...she's got bigger and stronger…” (Mother, participant 10, 8-year-old female, Medium Symptom Burden subgroup)

“...like in like second year, maybe a bit in third year. I would have, um, had to maybe sit out a few PE's or something, but it's not as bad, my knees aren't as bad as they were like then, but I used to have to maybe sit out, you know, like a match or something” (Participant 3, 15-year-old male, Low Symptom Burden subgroup)

“if you have asked me 3 years ago, our main things was her painful legs, whereas now there are so many other things going on with her, in different systems, that I feel so much of her is affected.” (Mother, participant 15, 6-year-old female, High Symptom Burden subgroup)

The impact of fluctuating symptoms can affect physiotherapy management, described as holding back progress by one adolescent:

“like my symptoms kind of change up, like one day. My hips will be really bad. And then the next week, I'll be something else completely different. So it's like really hard to gauge. Like when I go to physio, it would be like once every couple of weeks. So a new problem would crop up.” (Participant 17, 17-year-old female, High Symptom Burden subgroup)

For another, physiotherapy management helped parents manage fluctuating symptoms, describing how the physio could 'stay on top' of the changes:

"…the last time we went into physio, [child] had a really bad pain in her arm, and she's never gone into physio with a pain. And I was able to show the physio, and they massaged her and showed me how to massage and like I learned loads" (Mother, participant 6, 9-year-old female, Medium Symptom Burden subgroup)

5.11.1.3 Fear and worry about symptoms

Overwhelmingly, parents were more fearful or worried about symptoms both currently and in the future, compared to children or adolescents. Parents were also aware of other adults, such as teachers, who also expressed concern about their child's symptoms. Parents wanted to plan ahead, to prepare to manage future episodes, or the threat of symptoms occurring. This subtheme is explored in the quotes below, from parents:

"they do worry about her because sometimes, when she's on the yard, if she gets tired, she goes onto this bench there, but she'll shut herself away from her friends and stuff." (Mother, participant 15, 6-year-old female, High Symptom Burden subgroup)

"...as she's growing, I would love her to dip in and out of physio…like I'm always like, what's gonna happen as she gets older? That's what I get anxious about in her teenage years. Or like her hormones. Cause I know the anxiety as well. Like, I'm worried about like what's gonna happen later" (Mother, participant 6, 9-year-old female, Medium Symptom Burden subgroup)

"The only thing would be in the back of my head is, I suppose just how, you know, you'd love to have, to be able to see into the future to see where we are going to end up with it..." (Mother, participant 1, 6-year-old, Low Symptom Burden subgroup)

I have read up a bit, but I have never been sat down and spoke unexplained or spoken to by a doctor to tell me this is exactly what it is. All it was the last time was, is, oh, we'll do [group intervention], and I brought him every time he had to go and went for the reviews, which was grand... but really, I don't understand what it is…How will this affect the rest of his life going forward as a, as a teenager? (Mother, participant 16, 9-year-old male, High Symptom Burden subgroup)

Parents worry about not being able to protect symptoms such as injuries, such as when adolescents spend time with their peers:

"Like even when he goes over to friends' houses, you would be worried because this lad is going to do himself an injury now because this is the biggest thing that happens is the injuries. And you're like, right, he's not back for about five hours and to come back and like, oh I hit off this, I hit off that "(Mother, participant 12, 16-year-old male, Medium Symptom Burden subgroup).

5.11.2 Theme 2: Symptoms shape lives

"...if I had an employer, I'd be fired to put it this way…"

5.11.2.1 Impact on family Life

Children, adolescents, and parents had different perspectives about how their family life was impacted by symptoms. Children and adolescents focused on pain, or tiredness which was worse after play, after school, or at night. Some parents felt that home was where impacts were acutely felt, a place where the true nature of symptoms could be expressed.

"It [pain] makes me upset, and I come down to mom" (Participant 1, 6-year-old female, Low Symptom Burden subgroup)

“It’s so sore in my back… um, when I’m playing with my Lego” (Participant 16, 9-year-old Male, High Symptom Burden subgroup)

“...sometimes when I come home from school, I'll be too tired to function, so I'll have to go and, like, have a nap in the midday, and then I won't be able to sleep, like, the rest of the night.” (Participant 17, 17-year-old female, High Symptom Burden subgroup)

I can get very tired very quickly. Um, and I think I get kind of like; I get angry about it, and I bring it out on people that I don't really wanna bring it out on. (Participant 12, 16-year-old male, Medium Symptom Burden subgroup).

“They’re flatlining when they come home, they’re tired, they’re sore...” (Mother, participant 12, 16-year-old male, Medium Symptom Burden subgroup).

Parents explained the impact on their occupations, which ranged from managing time off for appointments, to career changes. Some had changed their working hours to part-time, whilst one parent went further to describe how they felt a need for a career change where one parent could work from home to support their child’s symptoms, experiencing relief if changes could be made:

“once I’m in work, I’m in work. now look, there’s always going to be times I’ll have to take time for appointments and stuff, but I really don’t mind, as I’m happy to take whatever is there...’ (Mother, participant 15, 6-year-old female, High Symptom Burden subgroup).

“And she [Mother] in the main has dedicated, actually dedicated her life for quite a few years to navigating the medical and the, uh, educational authorities …. how has it impacted our life? Well, it's been a full-time occupation...” (Father, participants 7 & 8, 11-year-old and 13-year-old males, Medium Symptom Burden subgroups)

“by profession, I was a bank manager, financial consultant, broker type person. And as soon as the kids started getting diagnosis, I changed” (Mother, participant 11, 10-year-old male, Medium Symptom Burden subgroup)

“like [adolescent] needed to be off today, and I'm here and it's not a big, it's not a big thing.” (Mother participants 7 & 8, 11-year-old and 13-year-old males, Medium Symptom Burden subgroups).

Some parents were participating in adult education and frequently missed deadlines for the submission of written work or assignments:

“I have my college work coming in and I have assignments and all and I'm gonna be either late or I'm gonna miss me class...” (Mother, participant 16, 9-year-old male, High Symptom Burden subgroup).

The chronicity of symptoms on the same family was evident:

“We have to adjust all the time… have been for a long time, to be honest’. (Mother participant 16, 9-year-old male, High Symptom Burden subgroup).

Managing appointments such as weekly physiotherapy or occupational therapy sessions required facilitation of employers, such as the provision of parental leave, and if appointments were in tertiary centres, this involved substantial travel away from home:

“like last year I took parental leave on Fridays to enable [son] to do the [Occupational Therapy] session.” (Mother, participant 11, 10-year-old male, Medium Symptom Burden subgroup)

“I've appointment after appointment, whether it's, even the time we were going to [Tertiary Children’s Hospital] every week. And then you'd have the paediatrician here, GP…It's just like, you wouldn't be able to, if, if I had an employer, I'd be fired to put it this way. So I kind of just parked, getting back to work fulltime...” (Mother, participant 1 &

14, 6-year-old female Low Symptom Burden subgroup, and 13-year-old female, Medium Symptom Burden subgroup)

Occasions such as Christmas, or going on family holidays, are recalled as families adapt to cope and express some element of guilt, 'we didn't really get it', reacting to a situation with some disbelief:

"..as time has gone on there are stomach problems, bowel problems, swallow issues, so she's on level 2 thickener for all her drinks, her food is awful, she literally eats four foods and that is it…it wasn't worth doing that to her [attempting a new food at Christmas time] either so it's not worth doing that and her level of pain is worse" (Mother, participant 15, 6-year-old female, High Symptom Burden subgroup).

"We went on holidays to Disneyland, um, a few weeks ago. And we didn't really get it, they said strollers for up to six years old, but I almost needed, wanted a stroller for [participant 6] cause she got very bad back pain, crying with back pain by the end of the first day. Her little sister was running around" (Mother, participant 6, 9-year-old female, Medium Symptom Burden subgroup).

Parents often compared siblings, and how difficult this could be.

"I took them to the sand dunes, which I probably didn't really think through….and you know, like her little sister is like jumping off them okay. And rolling in sand and [participant 6] is afraid…. and upset because she can't do what a five-year old's [sibling is] doing…and then when she did, she hurt her foot cause it was also soft sand, And I didn't think that through. then [younger sibling] couldn't understand why [participant 9] was upset and not wanting to play and they were fighting and yeah, like they're just different, aren't they? They're just different" (Mother, participant 6, 9-year-old female, Medium Symptom Burden subgroup).

“Like [his sister] is really strong in everything that she does…. a lot of frustration would've come up around his siblings especially his sister, who is really out there, really strong for her age actually, and loud and just a different personality…He does get very annoyed. Like I know he does. He, he just wants to be the best and he's competitive and he does feel held back. I know that. But like we, we wouldn't name that as hypermobility. It’s just...” (Mother, participant 9, 8-year-old male, Medium Symptom Burden subgroup)

Parents were also better informed to help other hypermobile siblings who may have been struggling with similar issues like handwriting, or felt better able to cope with younger siblings as they had been through it all before:

“One of her brothers he's very, very bendy and even as a baby, probably a little bit stronger now, but he's extremely bendy, even more so than [participant 10] I would say. The older boy, um, oh, he was waiting a long time for this pen license in school, and he was still on the pencil. It was so silly. So I told [the teacher] that [participant 10] had hypermobility and maybe he [sibling] does too and maybe just give him a pen” (Mother, participant 10, 8-year-old female, Medium Symptom Burden)

“To make sure that [participant 1] doesn’t go through in fifth and sixth class [go through similar issues to older sibling, participant 14] and whether puberty is a trigger for that or whether a really bad viral infection is a trigger for it, or whether it's just hypermobility at that age, you know, with puberty, I don’t know?” (Mother, participant 14, 13-year-old female, Medium Symptom Burden subgroup)

5.11.2.2 Impact on schooling

Children and adolescent participants explained the different ways that symptoms impact their schooling. Pain or fatigue with handwriting was commonly bothersome and affected the ability to keep up with schoolwork, parents were also aware of this, and noted a discrepancy between verbal and written work, or how using technology had helped:

“Sometimes when I'm writing, my hands get sore or tired...” (Participant 5, 9-year-old female, Medium Symptom Burden subgroup)

“My back is sore when I’m on the chair…” (Participant 16, 9-year-old male, High Symptom Burden subgroup)

“if he's writing any length at all, like his fingers get tired, his handwriting wouldn't be brilliant, you know, whereas he can fly on the laptop “(Mother, participant 2, 13-year-old male, Low Symptom Burden subgroup)

“for his verbal, how articulate he is and the level of ideas he would want to convey, he can't keep up with that [with his handwriting].” (Mother, participant 11, 10-year-old male, Medium Symptom Burden subgroup)

Exam years are supported by school, but the experience can be difficult:

’’Third year would've been very hard. By the time he came with his exams, we had to get a special lady in and have a special room so he could get up and move around. And he literally, every 10, 15 minutes he was tossing about on a chair or standing up to sit the exams “(Mother, participant 12, 16-year-old male, Medium Symptom Burden subgroup)

5.11.2.3 Impact on peer relationships

Adolescent participants felt that they struggled to keep up with their peers, especially when spending time together walking, or doing activities. Making friends more aware of symptoms, was a strategy found to be helpful for some, whilst others felt that peers wouldn’t get it, and as they found it hard to understand, felt that trying to explain it to peers would also be a challenge:

“a lot of the time when I'm out with friends, it's usually walking about town and I often have to like, stop and like, like, have a break from like, walking around and doing

activities…um…because, like, walking for too long, it's just, it's painful on my knees and my ankles and everything, and I get really, really fatigued...” (Participant 17, 17-year-old female, High Symptom Burden subgroup]

“I think his friends are very aware, he's different so they don't push the boundaries. So like they see when he is slowing up, falling behind the group. So they'll actually just sit down when in the grass or wherever and then just chill and one of them will usually plonk down... (Mother, participant 12, 16-year-old male, Medium Symptom Burden subgroup)

“they just kind of don't really know, and I think they forget sometimes, like when they're planning stuff, they forget that there's a friend that can't really do that kinda stuff” (Participant 13, 15-year-old female, Medium Symptom Burden subgroup)

“.. it's just hard to, to explain it to people, like friends don't get it. Family doesn't particularly get it, you know, so you're just kind of, you learn to say the minimum to people and to just work out for them yourself as much as you can, you know?” (Mother, participant 4 & 5, 10-year-old female Medium Symptom Burden subgroup and 13-year-old female, Medium Symptom Burden subgroup)

Additional diagnoses such as neurodevelopmental diagnoses are reported by many of the participants. This adds an additional layer of complexity which affects their relationships with peers:

“It does stop him, yeah, it’s difficult. He’s left behind by the others (pause) you know?” (Mother, participant 11, 10-year-old male, Medium Symptom Burden subgroup)

5.11.2.4 Impact on activities

Team sports such as Gaelic sports and rugby, are a cultural as well as social activity, that is engrained in many communities in Ireland. As team ball-sports, they were often

experienced as a challenge for different reasons, mostly around fatigue and keeping up, but also the influence of recurrent injuries, and advice from health professionals:

"it did affect her when she was playing GAA. It wasn't really suiting her. And then we were probably maybe trying to push her in to keep going, but it's just not for her" (Father, participant 6, 9-year-old female, Medium Symptom Burden subgroup]

I do swimming and drama now... when I was younger, I did like camogie and football and stuff. And I was like really tired during that, and I injured easily... (Participant 5, 13-year-old female, Medium Symptom Burden subgroup)

"I kind of quit, like, camogie and football …. I was talking to my GP, and she said that, um, I just don't have, like, the joint strength. Like, I'm more likely to get injured and stuff. And like, last year, I had a good few injuries. I, um, the worst one was for, like, spraining my ankle during PE as well." (Participant 17, 17-year-old female, High Symptom Burden subgroup)

Changing to other sports and activities that are not as sore, or less inclined to get injured with, or can pace better are described by participants and parents:

"Yeah, I did my ligaments in my right ankle…and I was in a boot, that I got in [the]Emergency department. And then they thought I broke my kneecap. But now I go to my trainings for rugby. And I go to a gym, I go like three times a week. We [with peers] try to go, like, Mondays, Wednesdays, Fridays, and then if we want to go on the weekend" (Participant 18, 16-year-old female, High Symptom Burden subgroup)

Another sport, swimming, often encouraged by health care professionals, as it is non-weight bearing and thought to be less impactful on sore joints can also be challenging as parents describe challenges, they perceived to be due to weakness, or lack of awareness of body in space:

“she just couldn't keep herself up, the muscles, without the armbands, just couldn't keep herself up. she wasn't progressing with all the toddlers, so she was coming away really like, upset all the time.’ (Father, participant 6, 9-year-old female, Medium Symptom Burden subgroup]

” I just think he couldn't actually control where his legs went. Like he couldn't, and he knows he's a good swimmer and he knows that he's able, but he couldn't, uh, turn his legs the right way. Like they just kept bending, like they kept telling him to straighten it up. I just think that was really hard for him’ (Mother, participant 9, 8-year-old male, Medium Symptom Burden subgroup)

Some parents would try to inform coaches about hypermobility, but this wasn’t always straightforward, with a lack of understanding by a coach, and a parent, choosing not to fight every battle:

‘[the swimming coach] ‘oh, that's nonsense’…I was like, okay’ (Mother, participant 9, 8-year-old male, Medium Symptom Burden subgroup)

The juxtaposition, whereby children are active during the day and in pain that night is a conflict for parents. Parents describe a pattern of play, involving intense activity which is a source of joy, but followed by a sense of ‘pay-back’ as a parent struggles to manage nightly, multi-joint symptoms, which are described wearily by one parent:

“And um, she's fine, see, it's hard, because sometimes you're looking at her flying around the place with her cousins and having a great time. Then you put her to bed and it's like she'll come down, she's complaining … she has a headache and sore back, sore legs, sore behind the knees, that’s every night.” (Mother, participant 1, 6-year-old female, Low Symptom Burden subgroup)

Parents, children, and adolescents often modify activities, or change to a lower impact activity, or practice pacing, a concept often used in management, or resolve to keep going, however symptoms are never far from the mind:

'We don't not do anything. We still do it, but we always know.' (Mother, participant 12, 16-year-old male, Medium Symptom Burden subgroup)

"[Handwriting] hurts my hand… [I just] keep going" (Participant 16, 9-year-old male, High Symptom Burden subgroup)

5.11.2.5 The impact of Covid-19

During the pandemic of Covid-19, school and work closures forced families into new routines, which had many impacts. Many families reported that symptoms actually improved during this time. Most adolescents noted that they had more flexibility in their routines, studying and doing lessons on laptops allowed them to stand and walk around more than usual:

"She was more active, funnily enough because my parents only live about 5 mins away, so as I used to say to her, we have to do meals on wheels, so I would cook for Mam and Dad and we would deliver it to their porch, but I made her cycle when we were doing that. The funny thing about that is now, she was doing that then, but she wouldn't be able to do that now, In that sense everything I feel has worsened. I try the short walks to the supermarket and things like that, if she does a high level of activity, she will really suffer for that, she's wrecked and she's sore." (Mother, participant 15, 6-year-old female, High Symptom Burden subgroup)

"The way my school did it, they had like online meetings like this, but like, uh, we still had the break between classes. Like they gave five minutes between class, but that I was able to walk around and stuff. You didn't have to have the camera on all the time, so I could

like, I could stand up and walk around in the middle of the class and, uh, like move..." (Participant 12, 16-year-old male, Medium Symptom Burden subgroup)

Another parent described how with some resources set up at home, her sons did class on their beds, sitting, lying down, which was a lot easier than sitting in hard chairs, reporting how without handwriting, their grades went up, there were less painful episodes:

"So I had everything at home. I had slope boards and wedge cushions before I could put them into the school. And so we had all of those ourselves, the iPads, their laptops, and we had things set up at home, you know... homework on beds...class on beds, sitting, lying down, looking at a phone up in the air or a stick holding it" (Mother, participants 7&8, 11-year -old male Medium Symptom Burden subgroup and 13-year-old male, Medium Symptom Burden subgroup)

Some therapy resources continued online, with one parent noting how physiotherapy exercises were done on video, which 'kept them going'. However, others recall how accessing services was difficult and that was very hard, especially for those where symptoms may have escalated, the flip side being that with less schooling demands, some of the 'pressure' was off:

"I was kind of just like my POTS was bad...and like my joint pain was kind of like constant and I've was like out of breath a lot… like during Covid I got diagnosed with POTS." Participant 14, 13-year-old female, Medium Symptom Burden subgroup)

"I think in a way it was difficult because we knew [adolescent] was not well and we still didn't know what was going on. But having said that, the fact that there was no pressure on us to be at activities to be at school took an awful lot of pressure off" (Mother, participant 14, 13-year-old female, Medium Symptom Burden subgroup)

5.11.3 Theme 3: Care pathway challenges

"[I don't know] where we should be going, and what we should be doing".

5.11.3.1 The search for management of symptoms

Parents described their encounters with the healthcare system with some experiencing feelings of frustration as they set off on a path, only to be abruptly halted, left wondering where next, or feeling misunderstood, as illustrated in the quotes below:

"...They just see it as, just double jointed. It's nothing. Do you know, whereas the likes of [participant 13] gets very frustrated then, you know, cause it's something for them, do you know what I mean?" (Mother, participant 13, 15-year-old female, Medium Symptom Burden subgroup)

"I feel like it's not really understood too much, like even my GP, so I just feel like stupid pushing it sometimes." (Mother, participant 6, 9-year-old female, Medium Symptom Burden subgroup)

"A GP would've had no knowledge about this at all. Okay. So at the start she was like, you have two healthy children. What's wrong with you?" (Mother, participant 4 &5, 10-year-old female Medium Symptom Burden subgroup and 13-year-old female, Medium Symptom Burden subgroup)

Some parents recall a moment when they perceived that symptoms were 'believed' or validated, and they felt understood by health care professionals, and the relief this brought:

"I think that day when [Dad] came back and said he was talking to somebody about hypermobility, it was, it was like, oh, you know, it's, she's believed, I suppose, is the word. 'Cause we obviously believed her 'cause we're living it, but her having all her injuries and bending this way and that way and the pain afterwards, you know, you know, we know

people don't see pain, other people… So, oh, it was great. It was great. It was actually brilliant" (Mother participant 18, 16-year-old female, High Symptom Burden subgroup)

Participants and parents describe engaging with healthcare professionals like physiotherapists, talking about complying with exercise programmes, and finding them helpful, or offering insight into why they felt they hadn't worked so well:

It [joint pain and ankle instability] used to be a bigger problem before he started doing his exercise with [physio]. He's used to go over quite a bit, whereas now, I don't hear about it, I'll be honest with you. (Mother, participant 2, 13-year-old male, Symptom Burden)

"…they [ankle pain] used to bother me a lot more back then, but now they don't really bother me as much. I've built, like, stronger [muscles]... so the exercises and stuff, so, yeah" (Participant 2, 13-year-old male, Low Symptom Burden subgroup)

"[the paediatric physio] gave us really good advice and he said, look, the best thing that you can do if you're, if he's remotely into sport is to do some martial art. Um, because that's going to really help him all through primary school, you know. It'll boost his confidence and it'll help to kind of mitigate, you know, some of these pains and so on. So anyway, luckily for me, um…. (participant 3) loves sport…. I think he feels and he knows mentally… That, that exercise is just really good for him. I think he; he knows because that's the way he was raised as well, that if he ever has a problem with something or if he gets overwhelmed, you know, you know, just with general kind of problems in life or, you know, things like this, that exercise is actually always a very good way to. Keep your mind in your head" (Mother, participant 3, 15-year-old male, Low Symptom Burden subgroup)

"Um, physio is great, but I think sometimes they push them a little bit too far and it makes your pain worse. And then, um, you're not really gonna get any better. You just get, kind of put off, cause there's, it's too much for your body. They're not really doing it in the

steps. And a lot of physiotherapists aren't really aware of it" (Participant 13, 15-year-old female, Medium Symptom Burden subgroup)

As many participants were under several different teams, having different investigations, they felt pressure to connect teams, feeling a sense of frustration:

"I just said someone needs to either pull everything together and figure out what this, cause they [a different tertiary service] think he has some genetic thing... (Mother, participant 16, 9-year-old male, High Symptom Burden subgroup)

Connecting services and seeing their children as a whole person was also expressed in the quotes below as parents felt that the benefit of individual health care professional encounters was diminished without a team or holistic approach to care:

"You know, I don't have a medical background, so I make mistakes, but I would love to have somebody coordinating care.' (Mother, participants 4 & 5, 10-year-old female. mediums subgroup and 13-year-old female, Medium Symptom Burden subgroup)

"I think the biggest thing is to have a holistic view. Like, and instead of, like, say for me now as a parent, I find each and every individual amazing, but I'd love it be more of team that they understand that this isn't just cardiology, this isn't just… or is there someone that can be the link between all of those consultants and physios, you know... ..And yeah, it needs to be holistic. Um, there needs to be more holistic care like, you know. And I think connected care is the best..." (Mother, participants 1 & 14, 6-year-old female Low Symptom Burden subgroup and 13-year-old female, Medium Symptom Burden subgroup)

5.11.3.2 Access to resources

The accessibility of resources to support symptoms, was a focus of parents in this study. Resources came in all forms. Parents often saw their role as a resource for their child, and

the need to be there, which was more acutely felt by parents who might have their own health issues:

"*I also think that, um, parents have a really huge role to play in a way" (Mother, participant 3, 15-year-old male, Low Symptom Burden subgroup)*

"I do a lot of reading and I do a lot of research as much as I can.' (Mother, participants 4 & 5, 10-year-old female, Medium Symptom Burden subgroup and 13-year-old female, Medium Symptom Burden subgroup

"I suppose the fact that he's an only child, and I can afford to put a load of time into him. So it's, you know, all the, I mean, the up and down, all the going to physios, you know, constantly minding him, watching him, trying to get assessments done" (Mother, participant 2, 13-year-old male, Low Symptom Burden subgroup)

"Unfortunately, because I have fibro as well, we, we have similar symptoms, which worries me with the fatigue and the pain and the. I think that …. it's very sporadic as well, you don't know where the pain is going to be on, you know..." (Mother, participant 17, 17-year-old female, High Symptom Burden subgroup)

"Like after the course [group intervention] she [participant 5], I... couldn't believe the difference. It was really obvious energy wise, even strength-wise, but like it was really hard then for a while, for about two weeks after the course, she kept up the exercises OK and then everything falls away, and then I ended up getting diagnosed with [chronic condition] during the year, so I've been unwell….So, If I was more on it, I think we'd be more physically active, you know? With her I'd have more energy to focus on it, like, you know" Mother, participant 5, 13-year-old female, Medium Symptom Burden subgroup)

Access to equipment, or the right environment to encourage activity which might be a source of help for a child was discussed. Some would take onboard management suggestions, even buying equipment, they might have seen in therapy centres:

"when you go to a PT or an OT session, and they give you a little tip… we got the peanut roll, and other bits of equipment, we have everything in like the gym bars are in the sitting room... they're down low... I was trying to get her [child] to do a pull up... you have your environment kind of set up that if there's an opportunity for movement...."" (Mother, participant 10, 8-year-old female, Medium Symptom Burden subgroup)

Access to and enacting changes in school required time and energy, and the responses of schools to take onboard suggestions was mixed:

"I always have to go in, meet with the principal and the other sub-principals and some of the teachers. And we usually go through everything. And then, um, I usually leave a note and they will ring me with any questions that they have" (Mother, participant 12, 16-year-old male, Medium Symptom Burden subgroup)

"Like we came in and told them that [child] needs movement breaks, and he needs support doing this and he needs to get a supported chair and it's, it just falls onto deaf ears. So, I think they need to be educated just as much as parents." (Father, participant 16, 9-year-old male, High Symptom Burden subgroup)

5.12 Discussion

This novel study explored the lived experience and impact of symptomatic hypermobility from the perspectives of children, adolescents, and their parents. Symptoms didn't always make sense. Children, adolescents, and parents also described how symptoms shaped their lives at home, at school and with their friends. Mixed perspectives were provided about the impact of the Covid-19 pandemic. Care pathway challenges were the focus of parents and to a lesser extent adolescents. Navigating a path to the management

of symptoms was varied. Social factors including parental health, parental occupation, family resources, access to care and support at school were explored. Disconnected services were seen as a barrier to navigating better pathways to care, a focus of parents in the study.

5.12.1 Making sense of symptoms

Participants in the current study stated that symptoms were difficult to comprehend, and difficult to explain to others. Previous research in adults with symptomatic hypermobility (JHS) reported that patients and health professionals felt that JHS was not widely understood amongst health professionals (328). An online questionnaire survey of paediatric physiotherapists also found that respondents were more confident in recognising hypermobility, compared to symptomatic hypermobility (JHS), with greater knowledge of articular rather than extra-articular features (329).

5.12.1.1 Uncertainty and diagnostic labelling

The current study demonstrated for the first time, the impact of this uncertainty on families. The difficulties surrounding the uncertainty of chronic pain have been explored in a cohort of adolescents with chronic pain (330). Their study found that health care professionals who were trying to talk to adolescents about pain, also felt 'helpless' at times (330). Understanding that pain is a biopsychosocial phenomenon is key, for all health professionals involved in the management of children and adolescents with chronic pain including patients with symptomatic hypermobility. Beyond pain and fatigue, uncertainty regarding symptoms is more profound. This study provides novel evidence of the negative impact of this uncertainty, as parents reflect and openly wonder, looking for reassurance.

Previous research reported that parents of children with symptomatic hypermobility found that diagnostic labels were meaningful to their child's care (305). In contrast, parents and children in this study weren't focused on terminology, or labels, although

they wanted to know what was going on. Parents questioned whether their child's symptoms were related to hypermobility, reflecting on the possibilities of connections. The changes in terminology over the past number of years have been highlighted in Chapters 2 and 3. Previous diagnostic criteria have found to be difficult to use in paediatrics (6). Uncertainty of diagnostic labels may impact on the therapeutic relationship as a lack of trust or collaboration (305). However, using a label to explain tissue involvement which is not clear could be unhelpful for the patient's understanding of their symptoms (331). Clinicians should validate symptoms, recognising the patient's experience and using established diagnostic classifications for symptoms such as pain and fatigue where possible (6).

5.12.1.2 Fluctuating symptoms

In the current study, adolescents and parents expressed how symptoms fluctuated. This was similar to adolescents with chronic pain and mental health symptoms including a participant with hypermobility, who described her symptoms to be unexpected and seemingly random, using the term 'a whirlwind of everything' (306). Unpredictable, fluctuating symptoms, and an imbalance, where no two days were alike, have been described in two studies of adults with symptomatic hypermobility (JHS/EDS-HT) (188, 203). In the current study, although fluctuating symptoms were reported, sometimes the fluctuation was considered a positive experience as there was an improvement or a resolution of their symptoms. This may reflect the younger age cohort in this study in comparison to other studies (188, 306). Changing symptoms also brought about challenges to some healthcare encounters, whereby a 'new problem would crop up' every couple of weeks.

Families also described how some healthcare professionals supported families to manage new symptoms. This reflects a similar finding where adult patients valued their physiotherapists as a partner to help patients manage their condition (301). Current policies in service provision may restrict the ability of a healthcare professional to provide

a longer term ‘partnership’ role, where treatments could be limited to a block of therapy. Opportunities to support patients in other ways such as telehealth, rapidly utilised over the Covid-19 pandemic, has the potential to extend therapy access and support for patients with chronic, fluctuating symptoms (332).

5.12.1.3 Siblings with hypermobility

A unique finding of the current study was that having a sibling with hypermobility provided insight to parents. In this study, three parents had two participants (siblings) in the study, and a further two parents reported children at home who were also hypermobile. Younger siblings may have benefited from parental experience, as parents pre-empted issues at home or at school. However, parents also reported worry and fear, that symptoms could worsen over time, or around puberty, as they may have already experienced this with an older sibling. Knowledge gaps exacerbate this fear and worry. Gaining better understanding of the nature of symptoms, and how they might evolve are important areas of research which are lacking and were important concerns of parents found in this study.

5.12.2 Symptoms shape lives

This study identified novel findings about the impact of symptomatic hypermobility on different aspects of life at home, at school and when spending time with peers. Importantly, this study found robust evidence of the considerable impact on parental occupations including a potential loss of earnings as some parents changed from full-time to part-time work to accommodate their child or adolescents care needs. Different aspects of family life were negatively affected, including family activities, holidays and family or national celebrations. The impact of symptomatic hypermobility from the perspective of the child, adolescent and parent has not been explored in previous qualitative research and these new findings are important in considering the wider impacts of symptoms that should be addressed in assessment and management.

5.12.2.1 Impact on family functioning

This study found that symptoms of pain and fatigue were the most commonly reported, and often the worst symptoms experienced by participants. This is a similar finding in a questionnaire study in youths with hEDS where pain and fatigue were commonly reported as 'the hardest part' of living with hEDS (155). Functional limitations are well documented in quantitative studies of children and adolescents with symptomatic hypermobility (20, 116, 155). Similar reports have been found in adolescents with Marfan syndrome, where leisure activities were perceived as too exhausting due to pain or fatigue (307). The current study provides a novel insight into the impact of symptoms on family functioning.

Spending time together as a family required greater planning and consideration of walking distances. Simple family activities requiring more strength and fitness highlighted differences between siblings, especially in comparison to younger siblings. Children with symptomatic hypermobility experienced anger, distress, or frustration at these times which in turn was upsetting for parents, 'we didn't really get it'. The impact of other symptoms, such as gastrointestinal issues, were felt acutely at special family celebrations, where sharing a meal together is the central event. Families found these events stressful and distressing for their child. Additional gastrointestinal diagnoses were common in children and adolescents participating in this qualitative study, particularly in the Medium and High Symptom Burden subgroups. This study has identified that patients in these subgroups may require supportive services from additional healthcare staff, such as dieticians, not commonly part of the multidisciplinary team in rheumatology services where these patients are most often seen.

5.12.2.2 Impact on peer relationships

This study found that peer relationships were impacted by symptoms. Terry et al., 2015 found that young adults felt that the fluctuating nature of symptoms exacerbated others' misunderstanding of JHS (188). Similarly, adolescents described how their peers don't

understand their symptoms. Previous research has found that children with symptomatic hypermobility (HMS) reported a higher frequency of need to rest, compared to a control group (132). In this study, increased awareness amongst a peer group enabled adolescent participants to keep up with their friends using extra rest breaks or pacing. However, lack of awareness and support meant that others experienced exclusion from activities. Being excluded from activities was noted by parents, in particular parents of children with additional diagnoses such as neurodevelopmental diagnoses, or allergies. Adolescents are particularly vulnerable to stresses that can contribute to mental ill health, which can often occur for the first-time during adolescence (333). Supporting children and adolescents in their physical and social development, including engaging with peers is essential to promote the physical and psychosocial health of children and adolescents into adulthood.

5.12.2.3 Impact on handwriting

Children and adolescents described the difficulties with handwriting at school, in all ages, and in all subgroups in this current study. These findings are in keeping with a survey study which reported 71% of participants struggled to keep up with handwriting including children with symptomatic hypermobility (334). Similarly, an earlier study in a tertiary paediatric rheumatology setting found that 40% of children with symptomatic hypermobility had problems with handwriting tasks (168). This finding highlights the role of assessing fine motor skills and managing handwriting issues. Limited research has found that use of a hand splint was not effective in improving handwriting speed or pain intensity (335). Although many children and adolescents now use technology instead of handwriting, especially into secondary school, handwriting remains a key fine motor skill. This is an area which deserves high quality research into the future.

5.12.2.4 Insights gained during widespread school closures

Data collection for this study occurred following the periods of restrictions due to the Covid-19 pandemic. The impact of school closures and social isolation was explored with study participants. In this study, school closures seem to have been a positive experience for some participants. Having more flexible timetables, and the ability to move around more during online classes were reported as positive. Some participants were more active, with parents noting an improvement in their symptoms as a result. Whilst others who may have been more unwell, found that accessing services was much more difficult during this time. Although no formal review has occurred in Ireland yet, a review in the UK found that school closures may have impacted the needs of children who were already vulnerable, more than others (336). This resonates with this study and is an important reflection and worthy of further research to consider the implications of future pandemics on those who are more vulnerable.

5.12.2.5 Healthy settings and adaptability

This study also points to advocating for policy and behavioural change to improve health in children and adolescents with symptoms of pain and fatigue especially. Improvements of symptoms were experienced by those who could move more freely, incorporate more activity in their daily lives, and experience a more flexible timetable to schooling. This 'settings' approach to healthcare including persistent pain (337) will be discussed further in Chapter 6, to propose a way to achieve this. The concept of flourishing has been recently explored in young adults living with chronic pain (338). Being able to adapt was reported as a potential contributor to flourishing and wellbeing, in young adults living with chronic pain (338). Health professionals, parents and teachers could support children and adolescents to develop problem-solving abilities to better manage their symptoms.

5.12.3 Care pathway challenges

This study did not set out to explore pathways to management, but parents frequently used the open question at the end of the interview schedule to describe the impact of their child's care pathway on symptoms. Parents recognised that they had a key role in this management, but that this could often place pressure on their own lives, in their occupations, or with their own health challenges.

5.12.3.1 Parental role in management

Involving family in the management of children with chronic pain has been found to have better outcomes in paediatric chronic pain research (339). This current study found that some parents played a more active role in the management of their child, for example taking notes during therapy sessions, purchasing equipment for movement opportunities in their homes, and providing resource to schools and primary care. However, different factors may have influenced the ability of parents to take on more active roles. Consideration of parental occupation, other demands such as further education, previous experience, access to resources, and good parental health impacted on the level of parental involvement in their child's management.

Consideration of positive parenting and social environment variables along with risk factors are thought to impact paediatric chronic pain adaptation and trajectories (340). A Canadian parent problem solving model for parents of youth with chronic pain focuses on positive and rational problem skills (341). It was found to be feasible and desirable by parents. Inclusion of family components are often advised for paediatric interdisciplinary pain management programmes, but specific treatments remain unclear (340). Developing similar programmes for parents and families of children and adolescents with symptomatic hypermobility, particularly those with greater symptom burden and less access to support and resources could facilitate better outcomes.

5.12.3.2 Health professional understanding

Previous research found that professional understanding was overall viewed with a negative appraisal by parents (305). Mixed appraisals were identified in this current study. Negative experiences were experienced by some parents in both primary care, and tertiary settings. The relief when their child's symptoms were finally 'believed' was reported by one family who described living with their adolescent, with a history of repeated injuries, and chronic pain, but previously others just couldn't 'see it'. Some parents described positive encounters with health care professionals, where physiotherapy interventions have had a positive impact on their child's symptoms.

Bell and Pearce, 2022, describe parents becoming experts and researchers (305). Similarly in this current study, parents also have become the experts in their child's care, however, they are frustrated and are keen for better awareness amongst health care professionals, as well as in schools and among sports coaches.

5.12.3.3 Connecting services and signposting for care

Parents expressed a need for better connections between services. With many children attending multiple services, parents recognised that despite positive, individual healthcare encounters, the lack of continuity of care impacted negatively on their overall experience. Better clarity for health care professionals, more established care pathways with clear, steps to management including specific indications for referral onwards could all contribute to a more holistic approach to management, identified as a clear gap in current management.

5.13 Strengths and limitations

The strengths of this study included the rigour used to enhance trustworthiness (325). The following steps were taken to ensure 1. Credibility, 2. Transferability, 3. Dependability, and 4. Confirmability. Credibility was ensured by using triangulation with

other data, debriefing with a peer, and adopting researcher reflexivity. Purposive sampling was chosen to fulfil the aims of the study by selecting cases with maximum variation to identify similarities and differences in the cohort (342). With the methods chosen in this study, the findings of this study cannot be generalised, but the transferability of the collected data was ensured by describing the sample in sufficient detail (Table 5.3). The collected data likely indicates the challenges experienced by children and adolescents with symptomatic hypermobility and their families. Dependability of the data collected, was ensured by a clear description of methods, data collection, analyses type used and interpretation. Confirmability was ensured by researcher regular consultation with researcher team, using an iterative process and use of triangulation of data.

Limitations of the study are noted. This study took place over a single time point, in children and adolescents aged 6-16 years and their parents, who were invited following their participation in Study II. Whilst this added to rigour, this also could be seen as a limitation, as this cohort were known to the interviewer, having attended on one previous occasion. The timing of some of the participants, towards the end of the school year, may have also influenced the impact of fatigue on participants. However, although reference was made to the end of the school year in one adolescent, other reports were of generic fatigue, unrelated to a time of year.

Efforts were made to ensure that the child's voice was heard, along with adolescents and their parents, to offer insights direction from the child's own perspective (343). The interview guide was refined following the pilot study, where simple language and a flexible approach was emphasised. Although face to face interviews were originally planned for, the movement to an online platform was familiar to families following the COVID-19 pandemic, when use of online platforms for education was common. Whilst the third theme which explored care pathway challenges reflected only parents' and adolescents' lived experience, this could be construed to represent a family narrative when observed through the biopsychosocial lens (31). Even though children were happy

to engage with the researcher, using more creative formats such as drawing, crafts or conducting research in different settings could be considered in future research to capture the child's perspective more fully (343).

5.14 Summary

This qualitative study is the first study to explore the lived experience of symptomatic hypermobility from the perspective of children, adolescents, and their parents. Use of a robust and rigorous methodology enhances the trustworthiness of the results. Furthermore, these results from Study II and Study III are integrated in the final Chapter of this thesis, to provide different perspectives on the same phenomena. This study found that participants expressed a need to make sense of their symptoms. Uncertainty of symptoms, was further compounded by fluctuating symptoms that were hard to explain to others, including other family members, and peers. Wide ranging impacts on family life were identified. The impact on parental occupation, and potential loss of earnings due to shifts from full to part time are unique findings. The changes which occurred during the Covid-19 pandemic such as schooling at home, were positive to some who found the flexible approach less impactful on symptoms, whereas others were negatively impacted from the reduced access to healthcare. Signposting is severely lacking for those on a hypermobility 'journey'. Development of improved care pathways would provide signposts to health care practitioners, families, and schools.

Study III Key findings

- Pain and fatigue are reported as the worst features of living with symptomatic hypermobility, but symptoms in other domains such as gastrointestinal and cardiology also have significant impacts in children and adolescents with symptomatic hypermobility
- Children, adolescents, and parents struggled to make sense of their symptoms
- Policy and behavioural changes within school settings could have positive impacts on symptoms
- Social factors including parental health, parental occupation, family resources, access to care and support at school are important considerations in assessment and management
- A lack of cohesion between services added to the burden of symptoms

Chapter 6 Discussion

6.1 Introduction and main findings

Joint hypermobility is encountered in healthcare settings, as part of a defined genetic syndrome, or, more commonly associated with a spectrum of symptomatology without a known genetic basis, termed 'symptomatic hypermobility' throughout this thesis. Similar symptoms are seen in the general population and causal links cannot be assumed (8), as the aetiology or the evolution of symptoms is still not known or well understood (1). Clinicians are challenged by this lack of aetiology, variability of symptomatology, issues surrounding recognition and diagnosis and the lack of evidence for the management of patients with symptomatic hypermobility.

Building on this research gap and progressing on previous research, the focus of this thesis is symptomatic hypermobility in children and adolescents. This thesis had three main aims: 1. to investigate the clinical characteristics of symptomatic hypermobility in children and adolescents, 2. to investigate if clinical subgroups could be found, and 3. to explore the lived experience and impact of symptoms. Three studies are included in this thesis, and the study designs were determined by the aims of the study. Study I, a systematic scoping review investigated clinical characteristics in symptomatic hypermobility, with a novel focus on developmental stage. Study II, a quantitative, cross-sectional study investigated clinical characteristics in children and adolescents with symptomatic hypermobility and explored if clinical subgroups could be found. Study III, a qualitative study, is the first to date to explore the lived experience and impact of symptomatic hypermobility from the perspective of children, adolescents, and their parents.

For the first time, a sequential explanatory mixed methods design was used to explore clinical subgrouping, with the integration of Study II and Study III. A staged approach to integration was used, whereby the results of each study were reported and discussed in the individual chapters (23). Table 6.1 details the procedure involved in the integration of Study II and Study III.

Table 6.1 Sequential explanatory design phase, procedures, and product (22)

Phase	**Procedure**	**Product**
Quantitative Data Collection (Study II)	Cross-sectional (n=80) • Structured Interview • Medical chart review • Clinical testing	• Categorial and Continuous data
Quantitative Data Analysis (Study II)	• Data screening • Group comparisons • Correlations • Cluster Analysis	• Descriptive statistics, missing data, normality, outliers, homogeneity of variance • Independent t-tests and Mann-Whitney U Test, Pearson, and Spearman's Correlation • Hierarchal Clustering and One-way analysis of variance
Connecting Quantitative (Study II) and Qualitative (Study III)	• Developing Interview topic guide • Purposive sampling from three clinical subgroups determined in Study II	• Interview pilot
Qualitative Data Collection (Study III)	Semi-structured interviews (n=18 children/adolescents and n=22 parents) • Email interview transcripts following interviews	• Data preparation • Data transcription • Reflexive approach
Qualitative Data Analysis (Study III)	• Coding • Theme development • Thematic analysis	• Reading and re-reading transcripts • Creating nodes and themes using mind mapping and theme piles • Grouping similar themes
Integration of Quantitative (Study II) and Qualitative (Study III)	• Interpretation and explanation of quantitative and qualitative results	• Discussion • Implications • Future Research

6.2 Changing symptoms

Study I of this thesis, a systematic scoping review, found evidence of a changing temporal pattern of symptoms as clinical characteristics were mapped using a developmental framework. This study was the first scoping review to map symptoms using a developmental framework and clinical characteristics were found to change with developmental stage. Castori et al., 2011, previously described a three-phase model, from marked ligamentous laxity in the first 'hypermobility phase', followed by a 'pain phase' starting in the second decade of life (90). The third 'stiffness phase' was marked by dramatic reduction in hypermobility (90). In contrast, Study I of this thesis found that pain was present in all developmental stages including childhood. Study II also found evidence of changing symptoms with developmental stage and similar to Study I, orthostatic intolerance was found in greater frequency in adolescents compared to children. Study III explored the nature of changing symptoms, which provided some insight into the nuances of changing symptoms. Some participants had improvements in strength and reported less fatigue and pain over time. Parents postulated that strength gains with age, or strengthening interventions may have helped.

Study III found evidence that changing symptoms were not always linear, and one of the subthemes constructed in Study III, was fluctuating symptoms. The changing nature of symptoms was commonly described by families, who expressed difficulties adapting to changing presentations. Similar findings were reported in a study including young adult participants who reported how their lives were disrupted by fluctuating symptoms and the 'cycle' of injury and recovery (188).

Evidence of an evolving clinical phenotype, and fluctuating symptoms, impacts clinicians and families. Paediatric clinicians already consider the role of growth and development throughout their clinical assessment, but this finding implies that clinicians should also consider that clinical characteristics in symptomatic hypermobility, may not be consistent across developmental stages, and can expect clinical findings to vary over time. Changing symptoms over time, may also require a more flexible approach to management and

service provision, which can be lacking. This thesis identified that families are more than aware that symptoms change, but the impact of these changes could be acknowledged better by clinicians, to support and validate symptoms, which may reduce the fear of threat and worry experienced by families. This finding also emphasises the need for future longitudinal studies to explore this further.

6.3 Uncertainty of symptoms

A novel finding of this thesis is the need for children, adolescents, and parents to understand their symptoms better. The link between hypermobility and symptoms is not well understood, and likely to be multifactorial, combining both intrinsic and extrinsic factors which in turn influence the expression of symptoms (19). This was the first study to report the negative impact of symptom uncertainty specifically in this cohort. This finding is in agreement with similar research in paediatric pain where difficulties in managing pain uncertainty in adolescents in rheumatology settings have been reported (330).

This thesis identified a number of factors which may be influencing this uncertainty. The literature describing clinical characteristics in symptomatic hypermobility is complex, diverse and spans multiple clinical domains. Diagnostic criteria used to classify hypermobility were varied, and the interpretation of criteria was inconsistent. Evidence of over seventy-five different measurement tools, including over eight different tools to screen hypermobility were reported in Study I. Diagnostic delay may also contribute to uncertainty. The median (IQR: Q1, Q3) length of time to recognition of symptomatic hypermobility, in Study II was 24 months (12 months, 48 months). Earlier recognition in paediatric symptomatic hypermobility has been emphasised (19). Better clarity and classification of clinical characteristics in children and adolescents with symptomatic hypermobility will provide a foundation to facilitate early recognition, improve understanding in health professionals and patients and may also help to alleviate the uncertainty for patients and their families.

6.4 Clinical subgrouping

Gaining a better understanding of the heterogeneity in the presenting symptoms of children and young people with symptomatic hypermobility, may also help clinicians to target treatment, which may improve outcomes for patients (20).

Fulfilling one of the aims of this thesis, children and adolescents with symptomatic hypermobility could be clustered into three clinically meaningful subgroups, using valid and reliable clinical measures, feasible in a clinical setting. These three subgroups were named according to their proposed level of care needs. Clinical subgroups have been identified in previous studies in children and adolescents with symptomatic hypermobility (85, 86, 116). However, to date, clinical subgrouping in symptomatic hypermobility has only been explored from a quantitative, or biomedical perspective. Studies in this thesis identified social factors such as parental occupation, and access to resources and support varied across subgroups. Exploring subgrouping using a mixed methodology, found that social factors are key considerations which impact on care needs.

This work provides new evidence and contributes to previous and ongoing work in the areas of paediatric pain (306, 330, 344), and heritable connective tissue disorders (307), and also addresses the paucity of qualitative studies in the area of paediatric symptomatic hypermobility (303, 305).

6.5 Biopsychosocial framework

This thesis recommends a re-focus on the social determinants of health in children and adolescents with symptomatic hypermobility, consistent with the sociopsychobio model of health, a dynamic version of the original biopsychosocial model (345). This version proposes that Engel's original biopsychosocial model is too fixed and that the three elements of the biopsychosocial model are more interdependent (345). Smart et al., 2023 suggests that physiotherapists should be involved in the development and integration of interventions that tackle social factors in the context of chronic pain conditions (31).

Barriers and enablers that influence healthcare professionals' adoption of a biopsychosocial approach in musculoskeletal pain have been carried out in adults with musculoskeletal pain (346) but further research is needed in paediatric settings where barriers and enablers may be very different.

6.6 Chronic pain

Chronic pain was highly prevalent, and pain was one of the symptoms along with fatigue that bothered participants most. Study I found that pain was reported in childhood, adolescence, and young adulthood studies. Specifically, different types of pain were reported in the literature, depending on developmental stage. Exercise-induced pain, myalgia, and arthralgia were reported in childhood, whereas chronic, recurrent pain was reported more frequently in studies in adolescents and young adults.

Pain dismissal has been described as a barrier to effective pain communication, in particular, when pain was deemed 'mechanical' in nature rather than due to an underlying rheumatological condition (330). Previous research in paediatric pain has commented that healthcare professionals may not have intentionally invalidated pain, which could be a factor in children and adolescents' symptomatic hypermobility, where aetiology is not always clear. Pain education in core rheumatology education and training in the UK is lacking (344). Researchers found that pain was positioned in educational texts as predominantly a 'somatic' feature (344).

The findings of this thesis provides a catalyst for change for children and adolescents and their families presenting with symptomatic hypermobility. Delivering transformative action in paediatric pain has also been emphasised by a Lancet Child and Adolescent Health Commission to make pain matter, make pain understood, make pain visible and make pain better to improve the lives of children and adolescents with pain (347). Clinicians should incorporate developmentally appropriate pain assessments, use the revised classifications of chronic pain (68), validate the patient's experience of chronic and perhaps fluctuating pain, and target those most impacted by their symptoms. This

may support both children and adolescents and health professionals, to establish a therapeutic alliance between families and healthcare providers, improving communication and reducing diagnostic uncertainty (330).

6.7 Fatigue

Fatigue was identified as one of the worst symptoms experienced by children and adolescents. Fatigue impacted on their lives at school, at home and with their friends. This is the first study to highlight the widespread impact of fatigue on children, adolescents and their parents using a qualitative methodology. Children and adolescents with symptomatic hypermobility had worse overall fatigue than children with other chronic health conditions (280). Fatigue can be associated with autonomic dysfunction, which is commonly recognised in adolescents and adults with hypermobile EDS (154, 348).

In agreement with others (87, 153) worse fatigue was strongly associated with lower levels of health-related quality of life. Previous intervention studies have not included fatigue as an outcome (124, 149, 349), and this was corroborated in Study I which found that measures relating to fatigue were reported less frequently in the literature than measures of pain and function.

Participants in the High Symptom Burden subgroup had significantly greater fatigue than participants in the Medium and Low Symptom Burden subgroups. Children and adolescents with symptomatic hypermobility (JHS/EDS-HT) who had greater fatigue, high pain levels, high incidence of multisystemic complaints and poor postural control, were deemed most likely to have a worse trajectory in one longitudinal study (116).

Fatigue should be assessed as part of a routine clinical assessment in children and adolescents with symptomatic hypermobility, using validated questionnaires such as the PedsQL™ Multidimensional Fatigue Scale (225) which was used in Study II. Involvement of the wider MDT including Occupational Therapists, may be key to optimise health

outcomes in those with more significant fatigue. Addressing fatigue in the wider context of schooling, family life and peer activities is an important consideration and further qualitative research is needed to explore these impacts further.

6.8 Movement - skills, strength, and physical activity

Motor skill proficiency was below average in 44% of participants, varying across clinical subgroups with those in the Medium and High Symptom Burden subgroups exhibiting worse motor skill proficiency. Poor motor skill proficiency and reduced strength were identified to have negative impacts on participation in sports, and participation in activities with families and peers in Study III. Participants were found to have lower levels of strength compared to age and sex normative data, which is of concern as paediatric dynapenia also predisposes to adverse health outcomes and is critical to enable the achievement of motor skill proficiency, required for participation in physical activity (290). These constructs were not included in a recommendation for the development of a core outcome set in a systematic review of outcome measures for children with hypermobility and lower limb symptoms (211). There appears to be a mismatch between outcome variables and components of management programmes where RCT's to date all include a strengthening intervention (21, 124, 157). Additionally, current physiotherapy management of patients with symptomatic hypermobility includes exercise as a significant component (4).

Combined with poor motor skill proficiency, the gap between this cohort, and those with higher levels of physical activity, strength and motor skills, will widen into the future (290). Targeting at risk groups within this cohort, in particular, overweight/obese groups, females, and children from lower socioeconomic status backgrounds is essential (350).

6.9 Additional diagnoses

Study III found that the presence of additional diagnoses had impacts such as increased social isolation, and reduced participation in social activities with peers or in team sports. Additional diagnoses were reported in 90.0% of included participants, and neurodevelopmental diagnoses were the most commonly reported, and diagnoses of allergy, gastrointestinal disorders, anxiety, primary dysautonomia and scoliosis were reported in greater than 10% of participants. Recent research also includes functional gastrointestinal disorders, anxiety and primary dysautonomia, as well as chronic pain, fatigue, and functional bladder disorders as six comorbidities which have been reported in previous cohort studies in greater than 10% frequency in paediatric hypermobility (6). The relationship between neurodevelopmental disorders and hypermobility is an emerging area of interest in the literature (351). Routinely screening for neuropsychiatric symptoms was recommended following a large review study, finding a strong association between HSD and hEDS and ADHD and ASD (183). However, any associations connecting hypermobility and additional diagnoses are complicated by inconsistencies in classification and assessment of hypermobility, study designs which are largely cross-sectional in nature, and predominance of descriptions of cohorts in tertiary, specialist settings.

Despite the lack of evidence in the literature, the presence of an additional diagnosis may influence interventions and are important to assess. Standardised diagnostic screening for neurodevelopmental and mental health disorders such as anxiety often take place in the community or primary care setting rather than tertiary settings therefore clinicians can lack access to standardised assessment results. Better communication between services by future use of electronic health records will help to disseminate important information. The coexistence of hypermobility with other disorders remains an area which requires future, high-quality studies and better understanding.

6.10 Multi-systemic features

Beyond the musculoskeletal system, clinical characteristics were present in widespread clinical domains, which varied with age. Dysautonomia, fatigue, sleep issues, and symptoms from urogenital and gastrointestinal domains were reported more frequently in adolescents. Cutaneous characteristics were reported in each developmental stage in the literature, but specifically, unexplained striae, and atrophic scarring were less frequent in children compared to adolescents in Study I and Study II. Cutaneous clinical characteristics were absent in the Low Symptom Burden subgroup found in Study II of this thesis, and present in greater than 20% of participants in both the Medium and High Symptom Burden subgroups. The presence of unexplained striae, and atrophic scarring were reported to occur in the most severely affected children and predicted greater disability in one longitudinal study of children with symptomatic hypermobility (116). Screening cutaneous features is a core element of paediatric rheumatology assessments, and features reported by participants were validated in medical records which increases the trustworthiness of results. The presence of skin and tissue abnormalities has been proposed as one of the key components in a new diagnostic framework for paediatric joint hypermobility (6). As assessments are largely subjective in nature, and therefore dependant on clinical expertise, determining the presence of skin involvement in clinical presentations may continue to remain challenging to many generalist clinicians outside of specialist settings. More objective assessments are needed, accessible to clinicians including physiotherapists in different settings, where symptomatic hypermobility is commonly encountered.

Urinary incontinence was reported in greater frequency in the High Symptom Burden subgroup, in comparison to the Medium and Low Symptom Burden subgroups. The presence of urinary incontinence has been found to impact quality of life (87, 352). Pelvic health is a speciality area of physiotherapy and may not be routinely screened. Consideration of screening for constipation, reported commonly in this cohort, as well as urinary incontinence is recommended (87).

Screening for multi-systemic symptoms is a key feature of a tertiary assessment, but there is a lack of guidance for clinicians in primary or community care settings (49). Multisystem clinical characteristics such as constipation and dizziness, can be present in the general paediatric population (8), particularly in chronic pain or fatigue cohorts (6). Assessments should be carried out using established diagnostic criteria (6, 68, 353, 354). However, using these criteria outside of specialist settings should be explored. In a paediatric setting, the involvement of a general paediatrician could be key in the management of symptomatic hypermobility in children and adolescents, to take a broad, holistic approach to the assessment and management of wide-ranging symptoms. Better understanding of clinical characteristics commonly seen in symptomatic hypermobility will support the assessment and management of patients with symptomatic hypermobility in primary and secondary care settings. This is supported by Ireland's 10-year health care plan, to ensure that the right treatments are provided to the right patient, ideally locally, reducing unnecessary interventions (15).

6.11 Hypermobility

Significant heterogeneity in the measures used to screen hypermobility was identified in Study I. Different cut-offs, and inconsistencies of standardisation of measures were identified. It has been established that recognising hypermobility in children is a challenge (19). In agreement with others (6, 355) a combination of measures, including the Beighton score with goniometry, the Lower Limb Assessment Scale (LLAS) and other measures of connective tissue laxity including the foot posture index, hamstring muscle length and the presence of cutaneous clinical characteristics were used in Study II of this thesis to gain a comprehensive clinical profile of individual connective tissue laxity.

Accurate measurement of hypermobility requires the use of measurement tools and standard reference sets for different populations (5). It has been postulated that using goniometry to determine the degree of joint range of motion, may be more sensitive than the simple dichotomous Beighton score, to help identify if greater range is

associated with the development of musculoskeletal complaints (356). Digital goniometers may offer an alternative to orthopaedic goniometers and have been found to be reliable in the paediatric clinical setting (357).

Study II of this thesis demonstrated that greater levels of hypermobility were not associated with increased pain, fatigue, or worse quality of life. As this study, similar to most studies describing the association between hypermobility and symptoms was cross-sectional, causality remains unknown (156). Pain was not linked to the level of joint mobility in a study of 286 Nigerian children aged 6-11years, whereby hypermobility was the norm (356). A recent narrative review ascertains that clinicians place greater focus on the pattern of hypermobility (5). Determining the pattern of hypermobility requires an assessment of every joint, which is in keeping with the use of a screening tool such as the pGALS musculoskeletal assessment (81), prior to using hypermobility screening measures. As hypermobility is common in children and adolescents, clinicians need to consider the clinical relevance of hypermobility, in the presence of symptoms or suspicion of a genetic syndrome (5, 19).

6.12 Family functioning

A novel aspect of this thesis was the exploration of family functioning in children and adolescents with symptomatic hypermobility. Study I highlighted the lack of qualitative studies in this area, which is limited to young adults only (188, 203, 301). There is a need to include the impact on family life and interpersonal relationships in clinical presentations (116). Study III of this thesis explored the impact of symptomatic hypermobility from the perspectives of the child and adolescent and their family. Furthermore, participants were recruited from Study II, to provide further insight into the clinical subgroups. Study III, a qualitative interview study, found that participants in the High Symptom Burden subgroup, who experienced the greatest severity of symptoms, reported more complex care pathways, multiple healthcare encounters and challenges at school, or in healthcare settings. Without adequate support and consistent signposting, a

heightened sense of fear and worry can compound the psychological and social burden of symptoms in this group. Better understanding of what symptomatic hypermobility represents for children and adolescents may lead to more systemic changes in healthcare and school settings, to reduce the social ramifications of symptoms particularly in those more impacted by symptoms.

6.13 Further considerations

The background of the Covid-19 pandemic presented a unique backdrop to this thesis. Symptoms were impacted during this time of widespread closures of schooling and social events such as sports and activities. Surprisingly, many participants reported an improvement of symptoms and alluded to the flexibility of schooling at home, where they reported that they were free to move, and that movement was integral to a reduction in their symptoms. This insight is a strong indicator to advocate for behavioural and policy change within the school setting to improve health in children and adolescents with symptomatic hypermobility. The results of this thesis hypothesise that children and adolescents with symptomatic hypermobility seek more movement throughout their day, and attention to every part of a school day, including active transport to and from school, time spent in PE and movement in the classroom setting could be considered to impact positively on their symptoms.

6.14 Critical analysis – strengths and limitations

The strengths of this thesis included the robust, rigorous methodology used in Study I, the scoping review. Over 1,600 abstracts were screened and over 900 full texts were reviewed to systematically clarify and interpret a considerable quantity of diverse literature to make it more accessible to clinicians and researchers. Of further note was the thorough approach to data collection from three sources including medical chart review, structured interview, and clinical measurements in the cross-sectional study. This

ensured that data could be triangulated and compared from difference sources, which increased the trustworthiness of the findings. A further strength of this thesis was the integration of the three studies. Clinical domains of interest identified in Study I, were used to screen multi-systemic symptoms during the structured interview in Study II. Furthermore, a sequential mixed methodology was used to connect Study II and Study III to explore clinical subgrouping from both a quantitative and a qualitative perspective. The justification for using a mixed methods approach was clearly described, and the guidance for Good Reporting of A Mixed Methods Study (GRAMMS) was followed (27). Issues of rigour were addressed in each study design, and both methods were described in significant detail. A potential limitation of using Mixed Methods in this thesis was added complexity using two different methodologies, and the need for extensive training in both approaches, in particular the analyses of both quantitative and qualitative approaches. Despite these challenges, using a mixed methodology drew upon strengths of both quantitative and qualitative designs, to provide an innovative approach to address the aims of this thesis. This allowed for richer insights into the identification of the clinical characteristics of symptomatic hypermobility, and clinical subgrouping.

Specific limitations in each study, are addressed in their respective chapters. The impact of the Covid-19 pandemic and the HSE Cyber Attack are discussed at the end of Study II. Limitations which were common to all stages are presented in this section. The context of growth and development was considered throughout each study in this thesis. Assessment of pubertal stage could have been used in Study II, to gain a more accurate assessment of stages of development (358). A pubertal stage assessment was not considered due to the extensive assessments included in the battery of testing. Findings in this thesis, in particular Study I where symptoms were found to change with age, which were corroborated in Study III, adds more value to consideration of including an assessment of pubertal status in future research.

Initially, a sample size estimation was calculated for ethics proposals, and during the design stage of the thesis. An estimation of n=300 participants was made, based on the

current clinic attendances in paediatric rheumatology settings where the research was undertaken across three sites in a tertiary children's hospital setting. However, two events, namely the Covid-19 pandemic, and following this the HSE Cyber-attack, severely curtailed recruitment. Although the final sample size was less than originally stated, planned analysis was still conducted and validation of the clusters will now be followed up in a new independent sample.

The cross-sectional nature of Study II means that causation cannot be inferred between any variable analysed in relation to another. Future longitudinal research is needed; however this thesis offers important insights into this population of children and adolescents in a tertiary paediatric rheumatology setting.

6.15 Recommendations for future research and clinical practice

Findings from this thesis support the need for longitudinal studies to explore symptoms over time. Gaining a better understanding of the evolution of symptomatic hypermobility is important to parents and could help to reduce fear and worry and diagnostic uncertainty. Future studies should stratify participants according to biological sex, age, and developmental or pubertal stage where possible. Outcome measures should follow strict protocols, to allow comparison amongst studies in different populations. As current studies largely take place in tertiary settings, future studies are needed in population-based settings, and primary and secondary care settings to explore clinical features and criteria in less specialised settings. Future research is needed to determine the stability of the clusters in an independent sample which was beyond the scope of this thesis. This will be conducted in an independent, well-defined sample to support the validation of the cluster solution (218).

Several clinical recommendations are made based on the findings of this thesis. Clinicians should use standardised assessments of paediatric hypermobility (54), and avoid the under or over diagnosis of hypermobility, taking into context the age, sex and ethnicity of the patient. Although the Beighton score is still recommended (6), using other tools such

as the Lower Limb Assessment Scale (62) is useful to help gain a broader view of multidirectional laxity, and focus on the lower limb where symptoms are commonly reported in children and adolescents. Adopting the pGALS (81) and PREMS (80) approach will help clinicians exclude other potential causes of symptoms. Clinicians should endeavour to use up to date classification and terminology in the area of paediatric pain (68). This will help to validate pain which is commonly found in symptomatic hypermobility. Screening for other system involvement and additional diagnoses is important and can help direct onward referrals and consider other treatment options where necessary. Future use of electronic health records will support the interconnection of services, an issue highlighted by parents in Study III. Better educational resources are needed for services outside of tertiary settings where hypermobility is commonly encountered, including primary care. Lastly social factors such as the role of parents, and the role of schools need to be incorporated into assessments and interventions. Providing resources to support children and adolescents with symptoms such as persistent pain and fatigue within a classroom setting are recommended.

Chapter 7 Conclusion

Symptomatic hypermobility is common in healthcare settings and can be challenging to recognise and manage. There is a need for clarity for clinicians and for families, to better understand symptomatic hypermobility in children and adolescents. This thesis found empirical evidence that symptoms evolve during the periods of childhood, adolescence, and young adulthood. Whilst symptomology can be complex, initial presentations are often musculoskeletal, and there is a growing awareness that addressing musculoskeletal health in childhood will reduce the long-term cost to society as persistent adolescent musculoskeletal pain is a risk factor for chronic pain in adulthood (359).

There is evidence to date that adults (76, 264, 360) and children (85, 86, 116) with symptomatic hypermobility may be separated into clinical subgroups. An innovative approach was used in this thesis, to investigate clinical subgrouping using a sequential mixed methodology to explore the impact of symptom severity within families. Novel insights were identified including the importance of social determinants of health, which may drive some of the challenges experienced by families. Re-focusing interventions to consider the important role that social factors play on health outcomes is recommended, and is consistent with a sociopsychobio model of health, particularly within the context of family life (345).

The prevalence of additional diagnoses in participants in this study was extremely high and this finding has significant implications for clinicians. A high incidence of neurodevelopmental disorders is consistent with emerging studies in neurodivergent adults, whereby joint hypermobility is proposed to mediate the link between neurodivergence and symptoms of dysautonomia and pain (361). Broad screening questions including those related to neuropsychiatry symptoms should be elicited in the patient history and may influence type and setting of interventions.

The third study of this thesis identified that children, adolescents, and their parents experience diagnostic uncertainty, and expressed a strong need to make sense of

symptoms. The threat of symptom progression and the fear of the future is a novel finding in this thesis and presents a unique viewpoint especially in the context of chronic pain. This is consistent with the suggestion that the presence of hypermobility leads to a feeling of vulnerability for injury and in turn experiencing more musculoskeletal pain (152). Previous research has only explored this using cross-sectional studies (301, 362) and further research should focus on the role of pain-related fear in children and adolescents with symptomatic hypermobility, and their parents. Addressing fear avoidance, and in particular threat perception, is pivotal to restore function (278). In light of the lack of discrete pathophysiological pathways and biomarkers, clinicians can help to address the role of pain-related fear earlier by the validation of symptoms such as pain and fatigue.

The patient's voice was central to this thesis and should be included in the future development of more targeted care pathways. This work will be disseminated through peer-reviewed publication, conference abstracts, presentations to clinicians, funding bodies and patient organisations. This thesis supports the use of the sociopsychobio model of health in the assessment and management of children and adolescents with symptomatic hypermobility. Enhancing education and training amongst clinicians, in particular paediatric physiotherapists working in this area should be targeted.

Whilst the findings of this thesis are exploratory, this research presents several novel findings with immediate implications for clinicians, ensuring the translational nature of this research. The findings of three subgroups is clinically meaningful and presents a pathway towards more targeted treatment and research.

Chapter 8 References

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Chapter 9 Appendices

Appendices can be found at the following link: https://hdl.handle.net/2262/109288