HEALTH-RELATED QUALITY OF LIFE IN MIDLIFE AND OLDER WOMEN
WITH HYPERMOBILE EHLERS-DANLOS SYNDROME AND HYPERMOBILITY
SPECTRUM DISORDERS

A Dissertation
presented to
the Faculty of the Graduate School
at the University of Missouri-Columbia

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

by
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Dr. Kari Lane, Dissertation Supervisor
DECEMBER 2023
The undersigned, appointed by the dean of the Graduate School, have examined the
Dissertation entitled,

HEALTH-RELATED QUALITY OF LIFE IN MIDLIFE AND OLDER WOMEN
WITH HYPERMOBILE EHLERS-DANLOS SYNDROME AND HYPERMOBILITY
SPECTRUM DISORDERS

presented by Linda Kay Anderson,
a candidate for the degree of Doctor of Philosophy,
and hereby certify that, in their opinion, it is worthy of acceptance.

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Dr. Lori Popejoy

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Dr. Tina Bloom

__________________________________________
Dr. Erin Robinson
DEDICATION

To be is to be perceived. And so to know thyself is only possible through the eyes of the other. The nature of our immortal lives is in the consequences of our words and deeds that go on apportioning themselves throughout all time. Our lives are not our own; from womb to tomb, we are bound to others, past and present and by each crime and every kindness we birth our future.

–David Mitchell, Cloud Atlas

I dedicate this dissertation to two individuals I am bound to throughout time. To my husband, Keith, I appreciate your love, confidence, gentle and patient caregiving, and careful proofreading of all manuscripts. To my daughter, Emily, I appreciate your love, sense of humor, belief in me, and for making me Swedish pancakes when I cried.
ACKNOWLEDGMENTS

I wish to thank the following individuals for their support and encouragement during this Ph.D. journey. I want to express my profound appreciation for my advisor and mentor, Dr. Kari Lane. Dr. Lane ensured I was well-prepared for comprehensive exams, tested my survey instruments, helped me analyze data, and taught me the value of brevity in writing manuscripts. I also want to thank my committee members, Dr. Lori Popejoy, Dr. Tina Bloom, and Dr. Erin Robinson, who were willing to learn about the poorly understood condition of hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders (hEDS/HSD). You supported me, a very non-traditional student, with your expertise and encouragement and challenged me to continue my passion for research and advocacy work. I also acknowledge Dr. Maithe Enriquez, my Community-Based Participatory Research certification advisor, as she was the first person to make me believe I could succeed in the Ph.D. program.

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I also express my heartfelt gratitude to the women with hEDS/HSD who participate in Ehlers-Danlos social media groups. Through my association with these online groups, I first identified the need for research on hEDS/HSD in midlife and older women. I also want to thank the moderators and administrators of the Facebook groups who graciously allowed me to recruit participants from their communities.
Most importantly, I thank the women with hEDS/HSD who participated in these studies. Their clear articulation of this community’s issues and needs was invaluable and will lead to more research on this topic. I promise to tell your stories.
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<td>BP</td>
<td>Bodily pain</td>
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<td>CHIEF-SF</td>
<td>Craig Hospital Inventory of Environmental Factors</td>
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<td>EDS</td>
<td>Ehlers-Danlos syndrome</td>
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<tr>
<td>EDS-HT</td>
<td>Ehlers-Danlos syndrome, hypermobility type</td>
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<td>FN</td>
<td>Function</td>
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<td>FT</td>
<td>Fatigue</td>
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<td>GH</td>
<td>General health</td>
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<td>hEDS</td>
<td>Hypermobile Ehlers-Danlos syndrome</td>
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<td>Hypermobility spectrum disorders</td>
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<td>ICF</td>
<td>International Classification of Functioning, Disability and Health</td>
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<td>JHS</td>
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<td>MDHAQ</td>
<td>Multidimensional Health Assessment Questionnaire</td>
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<td>Mental health</td>
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<td>PATGL</td>
<td>Patient global assessment</td>
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<td>Physical component summary</td>
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HEALTH-RELATED QUALITY OF LIFE IN MIDLIFE AND OLDER WOMEN WITH HYPERMOBILE EHLERS-DANLOS SYNDROME AND HYPERMOBILITY SPECTRUM DISORDERS

Linda Kay Anderson
Dr. Kari Lane, Dissertation Supervisor

ABSTRACT

An understudied area of gerontology is the impact of inherited genetic disorders as individuals age and how such conditions affect health-related quality of life (HRQOL) in older adults. Such is the case with hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders (hEDS/HSD). This condition represents a spectrum of heritable connective tissue disorders characterized by joint instability, tissue fragility, chronic pain, and multisystem dysfunction, leading to disability and poor HRQOL. Symptoms are more prevalent and severe in women than men, and early signs and symptoms are subtle and mimic conditions commonly seen in adults. Researchers have yet to identify a hEDS/HSD confirmatory biomarker, so individuals experience long diagnosis delays. Researchers have conducted most hEDS/HSD studies on young adult samples, so little is known about its clinical presentation, illness progression, and HRQOL impact in midlife and older women. This cross-sectional internet survey of women over 40 diagnosed with hEDS/HSD (n = 66, age range 40-87) measured this population’s demographic and health history using a custom instrument, symptom characteristics using the Multidimensional Health Assessment Questionnaire, environmental variables using the Craig Hospital Inventory of Environmental Factors, and HRQOL using the Short-Form 36. This study identified numerous comorbidities,
extensive diagnosis delays, and lower physical and mental HRQOL than age and sex-matched norms. This research also showed that environmental factors can significantly impact physical and mental HRQOL, a topic not yet explored in hEDS/HSD literature. This study yielded a model based on the International Classification of Functioning, Disability and Health (ICF) framework identifying HRQOL barriers and facilitators that extend the knowledge of the natural history and illness trajectory of hEDS/HSD in midlife and older women. These results may lead to earlier diagnosis, more effective treatments, and better physical and mental HRQOL.
Chapter One

Introduction

Hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders (hEDS/HSD) represent a spectrum of heterogeneous inherited connective tissue disorders characterized by joint instability, tissue fragility, chronic pain, and progressive multisystem dysfunction (Castori et al., 2017; Tinkle et al., 2017). The condition displays an autosomal dominant inheritance pattern, with symptomatic females outnumbering symptomatic males by 8-9:1 (Castori et al., 2010b; Chiarelli et al., 2019; Ricard-Blum, 2011). Although the specific molecular basis of hEDS/HSD is unidentified, some candidate genes have been suggested (Junkiert-Czarnecka et al., 2023; Malfait et al., 2017). Multisystemic symptoms progress in severity from childhood through adulthood, ultimately leading to functional disability and poor health-related quality of life (HRQOL; Berglund et al., 2015; Castori et al., 2010a, 2011; De Wandele et al., 2014).

The multisystemic and non-specific nature of hEDS/HSD symptoms leads to lengthy diagnosis delays (Anderson & Lane, 2021; Halverson et al., 2021; Kalisch et al., 2020), but no research has determined whether these delays impact health outcomes. Furthermore, although natural history studies in younger individuals with hEDS/HSD show an increased prevalence of symptoms with age (Castori et al., 2010a, 2011), the symptom progression in older adults, particularly women, needs further investigation (Anderson & Lane, 2023; Hugon-Rodin et al., 2016). Moreover, despite research showing the importance of supportive physical and social environments to individuals with hEDS/HSD (Clark & Knight, 2017; De Baets et al., 2017), research into the influence of the natural and built environments, policies, and services on health outcomes
in midlife and older women with this condition is absent. Finally, although researchers have identified an association between hEDS/HSD and HRQOL (Berglund et al., 2015; Castori et al., 2010a, 2011), there remains a knowledge gap in the sociodemographic, clinical, and environmental factors associated with physical and mental HRQOL in midlife and older women with hEDS/HSD. Understanding these factors would facilitate earlier diagnosis and improve health outcomes in midlife and older women with hEDS/HSD.

**Specific Aims**

This internet-based, cross-sectional study aimed to comprehensively understand hEDS/HSD in midlife and older women and identify factors influencing HRQOL in this population.

**Aim 1**

The first aim was to describe the self-rated personal, clinical, environmental, and HRQOL characteristics of midlife and older women with hEDS/HSD. This study administered a series of custom and standardized research instruments to measure sociodemographics, general and women's health history, current and recent symptoms, environmental factors, and HRQOL. These instruments were administered online with a study sample of women aged 40 and over recruited from social media groups. This information was analyzed and reported descriptively.

**Aim 2**

The second aim was to examine associations among personal, clinical, environmental, and HRQOL characteristics of midlife and older women with hEDS/HSD.
This study employed statistical methods to identify associations among the personal, clinical, environmental, and HRQOL variables identified in Aim 1.

**Aim 3**

The third aim was to determine the extent to which personal, clinical, and environmental characteristics were associated with physical and mental HRQOL in midlife and older women with hEDS/HSD. The data from Aims 1 and 2 were analyzed and reported using inferential statistics to determine the factors statistically associated with physical and mental HRQOL.

**Aim 4**

The final aim was to obtain participant views on barriers and facilitators influencing HRQOL in midlife and older women with hEDS/HSD. Optional open-ended, free-text questions were included in the cross-sectional survey to add additional context to findings from Aims 1 through 3 and create a better understanding of barriers and facilitators to HRQOL in this population.

**Background of the Problem**

**Pathophysiology of hEDS/HSD**

The Ehlers-Danlos syndromes, including hEDS/HSD, are hereditary connective tissue disorders (CTD) caused by faulty gene variants that alter the structural integrity of collagen fibers and the organization of the extracellular matrix (ECM) of connective tissues. (Alanis-Funes et al., 2022; Chiarelli et al., 2019; Royer & Han, 2022). Collagen comprises approximately 30% of the total protein mass in mammals and is the primary structural component of the ECM responsible for the integrity of joints, blood vessels, skin, and organ systems (Chiarelli et al., 2019; Ricard-Blum, 2011). The body-wide
aberrant collagen mechanics likely explain the multisystem manifestations and comorbidities associated with CTDs, including hEDS/HSD (Royer & Han, 2022).

Recent research suggests some non-genetic factors play a role in symptomatic hypermobility, including folate metabolism (Courseault et al., 2023) and proinflammatory factors that facilitate ECM degradation (Alanis-Funes et al., 2022; Chiarelli et al., 2019; Ritelli et al., 2022). The predominance of symptomatic females over males suggests a hormonal influence on joint laxity and symptom expression (Castori et al., 2010b; Hugon-Rodin et al., 2016; Maruyama et al., 2022). Researchers also suspect developmental and environmental factors have a role in the symptom expression of this complex syndrome (Castori, 2021; Chiarelli et al., 2019; Ritelli et al., 2022).

**Clinical Characteristics of hEDS/HSD**

Symptom progression in hEDS/HSD occurs in three general stages (Castori et al., 2010a, 2011). The first stage emerges in children, who may exhibit congenital contortionism, motor delay, and clumsiness. The second stage appears in adolescents and young adults, who may develop repeated musculoskeletal injuries and chronic, widespread pain. The third and final stage, characterized by age-related loss of articular hypermobility, increased pain, and multisystemic dysfunction, usually occurs when patients reach their late 20s and early 30s (Castori et al., 2011). However, few studies have addressed symptom progression after age 40 despite research showing an abrupt decrease in tissue elasticity in perimenopausal females (Luebberding et al., 2014; Palmer et al., 2020). As no studies have focused solely on midlife or older women, more research is needed about hEDS/HSD symptom progression and burden as women age, particularly...
considering patient reports of significant worsening of symptoms during and after menopause (EDS Awareness, 2022; Hagar, 2018; Laughlin, 2017).

**Diagnosis of hEDS/HSD**

Due to the unpredictable, non-specific symptoms and an undefined genetic basis, hEDS/HSD diagnosis must be obtained through the clinical criteria outlined by the 2017 International Consortium (Malfait et al., 2017). Symptoms of hEDS/HSD overlap with other disorders, and patients may be misdiagnosed with such illnesses as fibromyalgia, chronic fatigue syndrome, or a psychiatric condition such as anxiety, depression, or hypochondria (Castori, 2012; Hamonet & Ducret, 2017; Langhinrichsen-Rohling et al., 2021). The heterogeneity in hEDS/HSD symptom presentation and progression, the paucity of knowledgeable providers, judgmental attitudes towards individuals with unexplained symptoms, and healthcare system issues lead to frequent diagnostic delays and misdiagnoses (Anderson & Lane, 2021; Berglund et al., 2015; Castori, 2012; Hamonet & Ducret, 2017).

**Treatment of hEDS/HSD**

Randomized clinical trials to identify effective treatments for hEDS/HSD have been hampered by the low number and wide geographic distribution of eligible participants, a problem noted with research into other rare conditions (Gagne et al., 2014). Consequently, the evidence for hEDS/HSD treatments is limited, and most clinical care is focused on symptom relief, predominantly chronic pain and fatigue (Malfait et al., 2017). Other hEDS/HSD symptoms, including gastrointestinal, genitourinary, orthopedic, neurologic, and autonomic dysfunction, must be evaluated and treated by the appropriate
clinical subspecialty. Unfortunately, patients with hEDS often have disappointing results from symptomatic treatment (Tinkle et al., 2017).

**Health-Related Quality of Life**

Quality of life (QOL) refers to satisfying life conditions, general well-being, and the possession of sufficient resources to meet individuals' needs (Boggatz, 2016; Hörnquist, 1982). HRQOL is QOL in health states (Brummel, 2018; Karimi & Brazier, 2016). Researchers have consistently found an association between hEDS/HSD and HRQOL (Berglund et al., 2015; Mastoroudes et al., 2013; Palmer et al., 2019; Zeitoun et al., 2013). Recently, researchers in Italy and the US have used HRQOL to distinguish severity class and symptom cluster profiles in hEDS/HSD (Copetti et al., 2019; Schubart et al., 2019). These studies demonstrate that the number and severity of multisystemic clinical manifestations of hEDS/HSD significantly impact patients' HRQOL.

**Significance of the Study**

**Nursing Implications**

There is limited knowledge in nursing and the broader healthcare community about the natural history and symptom progression of hEDS/HSD in midlife and older women. As a result, undiagnosed midlife and older women with hEDS/HSD remain unidentified, increasing the likelihood of misdiagnosis, increased risk of iatrogenic injury, and failure to establish knowledgeable clinical oversight to optimize clinical function and HRQOL.

Few hEDS/HSD studies have included nurses on their multidisciplinary research teams, and even fewer studies have been led by nurses or have incorporated nursing theories or frameworks into their study designs. Since the understanding and management
of hEDS/HSD varies widely by medical discipline, nurses are uniquely positioned to bridge the gap between clinical specialties and view the issues from a more holistic, patient-centered perspective.

**Social Implications**

With the decline of joint hypermobility and the accelerated deterioration of body systems as a natural consequence of aging, hEDS/HSD in adults is often unrecognized and untreated, leading to increased disease burden on the patient, family, and society (Sinibaldi et al., 2015). As an invisible illness with few, if any, outward clinical signs, patients struggle to find support from friends, family, and the healthcare community (Berglund et al., 2010). This lack of support, pain, fatigue, and other manifestations of hEDS/HSD can lead to social isolation and poor quality of life (Berglund et al., 2015).

**Theoretical Framework**

The International Classification of Functioning, Disability and Health (ICF), a biopsychosocial model from the World Health Organization (WHO) that blends medical and social models of disability, provided the theoretical framework for categorizing this study's outcomes (World Health Organization, 2001). The ICF provides a standardized language that improves communication among healthcare stakeholders, facilitating comparisons across locations and disciplines and providing a coding schema for health information systems.

The universe of the ICF encompasses *health domains*, including the senses, mobility, and cognition, and *health-related domains*, such as social activities, education, and transportation. The ICF structures information about human functioning and its restrictions into (a) Functioning and Disability, comprising body functions and structures,
activities, and participation, and (b) Contextual Factors, comprising environmental and personal factors. *Body functions* refer to the physiologic and mental functions of body systems, for example, pain, sensory impairment, and anxiety. *Body structures* refer to the anatomical parts of the body and include such things as the eyes, brain, and blood vessels.

In the ICF, body functions and structures share a classification structure based on body systems. *Impairments* refer to deviations or loss of a body's function or structure. *Activities* refer to an individual's execution of a task, and an *activity limitation* is an individual's difficulty in executing tasks. *Participation* refers to an individual's involvement in a life situation, and a *participation restriction* refers to an individual's difficulty with involvement in life situations.

Contextual Factors include Environmental Factors and Personal Factors. *Environmental factors* are the social, physical, and attitudinal environment in which people live. Environmental factors have facilitators, including technology or access to healthcare, and barriers or hindrances, including financial limitations or poor social support. *Personal factors* refer to individual attributes such as age, gender, education, and clinical history and are internal influences on functioning and disability. While an important influence on health, the ICF does not formally classify personal factors due to cultural and social variability. The ICF domains and factors provide a structure for understanding health and health outcomes. Figure 1.1 displays this ICF framework.

The ICF establishes a common patient-centered and multidisciplinary language and systematic coding scheme for health states that facilitates the comparison of health-related data across locations, disciplines, and time. Rehabilitation clinicians have found the ICF a valuable tool to promote professional education and clinical reasoning skills.
Researchers have found the ICF a valuable framework for hEDS/HSD research because it is patient-centered, globally adopted, and appropriate for complex disabling conditions (Engelbert et al., 2017; Jacobs et al., 2018; Johannessen et al., 2016; Scheper et al., 2016). This framework broadens nursing's perspective of health and disability by moving from a traditional illness and disease model toward a social model of disability (Gómez-Salgado et al., 2018; Kearney & Pryor, 2004). The ICF framework promotes collaborative practice, making it useful in designing complex health interventions that cross traditional disciplinary boundaries (Kearney & Pryor, 2004).

Figure 1.1

*International Classification of Function, Disability and Health (WHO, 2001).*

This study adapted the ICF framework for functioning/disability and contextual factors associated with HRQOL in midlife and older women with hEDS/HSD. The Functioning and Disability domain of Body Structures and Functions included physical
symptoms and comorbid conditions. Activities and Participation included measures of HRQOL. The Contextual Factors in the Environmental Domain included variables related to the physical and social environment and assistive devices. Finally, the Personal domain included sociodemographic variables and clinical history. Figure 1.2 shows the proposed interrelationships among the ICF domains and categories and their impact on physical and mental HRQOL in hEDS/HSD.

**Figure 1.2**

Proposed ICF Framework for HRQOL in Midlife and Older Women with hEDS/HSD
Summary and Organization of Dissertation

This introductory chapter provided a broad overview of hEDS/HSD, health-related quality of life, and the specific aims of this study. This chapter also identified the social and nursing implications and current research gaps related to hEDS/HSD in midlife and older women. Finally, this chapter summarized the ICF as the theoretical framework for this study.

Chapter Two is a qualitative synthesis of diagnosis delays in hEDS/HSD. Researchers have long known of extensive diagnosis delays in individuals with hEDS/HSD, and a diagnosis of hEDS/HSD in older women may take many decades. Despite this, researchers have yet to study the exact reasons for these delays. This paper reviewed the existing qualitative literature on hEDS/HSD to develop a model of factors contributing to these diagnosis delays.

Chapter Three is a scoping review of the clinical trajectory of hEDS/HSD in older adults. Researchers' current understanding of hEDS/HSD natural history and clinical course is based on studies of young to middle-aged adults. However, studies have yet to specifically look at aging and age-related factors in hEDS/HSD as they apply throughout the lifespan. This literature review revealed high variability in symptom progression and outcomes, indicating the need for more research to uncover age-related factors that impact hEDS/HSD progression.

Chapter Four is a cross-sectional study with older women diagnosed with hEDS/HSD to determine the feasibility of an internet-based survey with this population. Results showed success in recruiting participants from Facebook support groups and overall satisfaction with the survey. Results suggested older women with hEDS/HSD
experienced high symptom burden and poor health-related quality of life, pointing to the importance of more extensive studies with this patient population.

Chapters Five and Six outline the methods and results of a cross-sectional internet survey study about HRQOL in midlife and older women with hEDS/HSD using the ICF framework. The primary aim was to identify factors associated with physical and mental HRQOL in this population. The secondary aim was to provide an overview of this population’s sociodemographic features, clinical history, symptom characteristics, and environmental conditions associated with HRQOL. Participants identified physical, social, environmental, and personal factors associated with HRQOL, including menopausal status, employment, number and type of comorbidities, symptom prevalence and severity, environmental barriers, personal knowledge, attitudes, and outlook.

Chapter Seven provides a review and summary of study results and places these findings in the broader context of existing hEDS/HSD research through an illustrative case study of one participant. This chapter also acknowledges limitations and examines the researcher’s positionality in this study. Finally, this chapter also outlines implications for clinical practice and research and discusses implications for the discipline of nursing.
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Chapter Two

The Diagnostic Journey in Adults With Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorders: A Synthesis of Qualitative Literature


Authorship Statement

Linda K. Anderson performed the topic selection and development, literature search, study selection, results synthesis, and drafted the initial manuscript. Kari R. Lane assisted in study selection and results synthesis and critically reviewed the manuscript for important intellectual content. Both authors approved the final manuscript for publication.
Abstract

Background. Researchers have identified lengthy diagnosis delays in patients with hypermobile Ehlers Danlos Syndrome and hypermobility spectrum disorders (hEDS/HSD), but the reason for these delays is unclear. Objective. This review seeks to synthesize the existing qualitative research about hEDS/HSD to understand the reasons for diagnosis delay. Data Sources. We searched PubMed, Scopus, CINAHL, Google Scholar, and Dissertations and Theses databases for all qualitative studies about hEDS/HSD that mentioned the diagnosis process. A total of 283 studies were retrieved, from which we identified 13 studies to include in this synthesis. Conclusions. The reviewers identified and organized diagnosis delay themes under four overarching categories: disease, patient, provider, and system. Disease factors included the nature of the symptoms and lack of a confirmatory test. Patient factors included psychological and emotional responses, seeing multiple providers, and receiving multiple diagnoses. Provider factors related to limited knowledge and attitudes. System factors included silo-based healthcare systems and bureaucratic barriers. Implications. Interventions targeting any single facet of diagnosis delay must consider the other factors to be effective. Research findings about difficult-to-diagnose conditions, including hEDS/HSD, must be communicated in a timely fashion to primary care clinicians. Providers must work across disciplinary silos to address multisystemic conditions in a unified fashion. Providers must also communicate empathetically with patients to avoid distrust and healthcare avoidance. Further research in hEDS/HSD is needed to identify and address the complex issues that lead to diagnosis delay.
Keywords: diagnostic delay; Ehlers-Danlos syndrome; hypermobility spectrum disorders; joint instability; joint laxity; qualitative research
The Diagnostic Journey in Adults With Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorders: A Synthesis of Qualitative Literature

Hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders (hEDS/HSD) represent a group of connective tissue disorders characterized by joint instability, tissue fragility, chronic pain, and multisystem dysfunction leading to disability and reduced quality of life (Malfait et al., 2017; Tinkle et al., 2017). Signs and symptoms are subtle and overlap with other illnesses, making diagnosis challenging (Tinkle et al., 2017). Studies show the time between symptom onset and diagnosis may be 20 years or more (Kalisch et al., 2019). The consequences of delayed diagnosis include iatrogenic effects of unnecessary tests, therapies, and surgical procedures, worse pain, more psychological distress, and poor health-related quality of life (Kalisch et al., 2019).

Diagnosis delays are common in other conditions as well, including Lyme disease (Hirsch et al., 2018), cancer (Anderson et al., 2009), axial spondyloarthritis (Lapane et al., 2020), and other rare diseases (Kliegman et al., 2017). Lapane et al. (2020) conducted a qualitative study of diagnostic delays in axial spondyloarthritis (axSpA). Similarities between axSpA and hEDS/HSD include: (a) prolonged diagnostic delays; (b) common, intermittent, and non-specific symptoms; and (c) lack of a confirmatory test for diagnosis. Lapane et al. (2020) identified four factors contributing to diagnostic delays in axSpA, including disease factors, patient factors, physician factors, and system factors. Because of similarities in diagnostic complexity between hEDS/HSD and axSpA, for this review, we synthesized our findings within this four-factor framework.
Objective

This review aims to examine the qualitative literature about patients with hEDS/HSD to understand their diagnostic journey and identify possible causes of diagnosis delays.

Materials and Methods

Study Design

Consistent with the process of qualitative research synthesis outlined by Sandelowski & Barroso (2007), this review will interpret and synthesize data contained in existing qualitative research, remaining faithful to the previous findings but providing a deeper interpretation of phenomena from the sample as a whole that we would not find in any single study. We report these results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009).

Search Strategy

We searched PubMed, Scopus, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Google Scholar, and Discover@MU: Dissertations and Theses between March 2 and May 21, 2021, for pertinent human, adult, English-language qualitative studies, combining the primary search terms, ehlers-danlos OR hypermobile* with the Boolean operator AND the secondary search terms qualitative AND diagnos*.

There was no restriction based on specified study aims. We also assessed the included studies' reference lists for additional pertinent articles.

Study Selection and Data Extraction

Eligibility Criteria

Studies were included if they met the following criteria:
- Qualitative or mixed methods studies with qualitative findings
- Published before the first search date of March 4, 2021
- Findings with statements about the hEDS/HSD diagnosis process
- Participants were diagnosed with hEDS/HSD or any previous analogous diagnoses including Ehlers-Danlos, hypermobility type (EDS-HT); Ehlers-Danlos syndrome, Type III (EDS III); hypermobility syndrome; and joint hypermobility syndrome (JHS)
- Adult participants (Note: We included one single-family qualitative case study that included adult parents and three minor children

**Study Selection**

After duplicate removal, the first author reviewed and excluded records that did not meet inclusion criteria based on title and abstract. The first author examined the full text of the remaining studies, which the second author subsequently verified. The two authors reached an agreement on the studies to include in this review.

**Data Analysis**

The first author abstracted data from the selected articles and documented the findings in an Excel spreadsheet, which was reviewed and verified by the second author. Information abstracted included full citation; year and country of study; study type; study objective/aim; sample size and description; and study findings related to diagnosis. We used an iterative, hybrid deductive and inductive approach to identify themes, using an initial subcoding method described by Saldaña (2016). We defined primary codes based on Lapane et al.’s (2020) four-factor framework for diagnosis delay, followed by an inductive process to determine the second-order tags. Subsequent coding cycles further
developed major themes and subthemes and identified emergent codes and themes that did not fit into the initial coding framework. The first author conducted the data analysis, which the second author then reviewed. The authors discussed coding and analysis conflicts until they reached an agreement.

We conducted methodological reporting appraisal using The National Institute for Health and Care Excellence’s (NICE) checklist for qualitative studies (National Institute for Health and Care Excellence, 2012). NICE developers acknowledge that qualitative studies have less clearly defined validity criteria; therefore, researchers must be flexible in determining study trustworthiness (NICE, 2012). For this reason, we excluded no studies from this review based on this methodological assessment. The NICE checklist consists of 14 items to assess theoretical approach, study design, data collection, trustworthiness, analysis, and ethics. We rated checklist criteria as (a) Met = all or most of the criteria were met, (b) Unclear = some elements of the criteria were unclear or not met, and (c) Not met = none or few of the elements of the criteria were met. For the mixed methods studies in this review, we assessed only the qualitative portion.

Results

Included Papers

Figure 2.1 shows our search results and study selection process following the PRISMA guidelines. The initial search yielded 283 studies. After duplicate removal, article exclusion based on title or abstract, and full-text review of remaining articles, we included 13 studies in this review.
Quality Appraisal

A consolidated summary of the quality appraisal results is shown in Table 2.1. Overall, the included studies were of high methodological quality according to the NICE criteria. The weaknesses included a lack of theoretical assumptions and methods.
rationale, insufficient discussion of triangulation and methods to guard against bias, and lack of clarity regarding the relationship between researchers and participants.

**Table 2.1**

*National Institute for Health Care and Excellence (NICE) Quality Appraisal Summary*

<table>
<thead>
<tr>
<th>NICE Criteria</th>
<th>Total studies (of 13) meeting criteria</th>
<th>Deficiencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is the qualitative approach appropriate?</td>
<td>13</td>
<td>No underpinning values/assumptions/theories discussed</td>
</tr>
<tr>
<td>2. Is the study clear in what it seeks to do?</td>
<td>12</td>
<td>No rationale or theoretical justification for approach or techniques used</td>
</tr>
<tr>
<td>3. How defensible/rigorous is the research methodology?</td>
<td>12</td>
<td>Lack of clarity regarding relationship between researcher and participant; no mention about study information presented to participants</td>
</tr>
<tr>
<td>4. How well was the data collection carried out?</td>
<td>13</td>
<td>No discussion of context bias considerations</td>
</tr>
<tr>
<td>5. Is the role of the researcher clearly described?</td>
<td>8</td>
<td>Insufficient evidence of triangulation; no justification for triangulation or lack of triangulation</td>
</tr>
<tr>
<td>6. Is the context clearly described?</td>
<td>12</td>
<td>Superficial discussion of findings</td>
</tr>
<tr>
<td>7. Were the methods reliable?</td>
<td>11</td>
<td>No indication more than one person conducted analysis; no evidence of participant feedback</td>
</tr>
<tr>
<td>8. Is the data analysis sufficiently rigorous?</td>
<td>13</td>
<td></td>
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<tr>
<td>9. Is the data 'rich'?</td>
<td>12</td>
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<tr>
<td>10. Is the analysis reliable?</td>
<td>9</td>
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<tr>
<td>11. Are the findings convincing?</td>
<td>13</td>
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<td>12. Are the findings relevant to the aims of the study?</td>
<td>13</td>
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<tr>
<td>13. Conclusions</td>
<td>13</td>
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<tr>
<td>14. How clear and coherent is the reporting of ethics?</td>
<td>12</td>
<td>Superficial discussion of ethical concerns, e.g., anonymity, consequences of research</td>
</tr>
</tbody>
</table>
Study Characteristics

We show included study characteristics in Table 2.2. Selected articles were published between 2012 and 2021 and included two doctoral theses/dissertations (Clark, 2012; Friedner, 2020), with the remainder published in peer-reviewed journals. Eight studies were performed in the UK (Bennett et al., 2021; Clark, 2012; Friedner, 2020; Palmer et al., 2016; Palmer et al., 2019; Pezaro et al., 2020; Schmidt et al., 2015; Terry et al., 2015) with four conducted at the same research center with several authors in common (Bennett et al., 2021; Palmer et al., 2016; Palmer et al., 2019; Terry et al., 2015). Two studies conducted at the same research center (University of the West of England, Bristol) appeared to draw participants from the same sample (Palmer et al., 2016; Terry et al., 2015). However, we included both studies in this review to ensure a comprehensive analysis of findings. Two studies from Belgium were conducted by the same research center with common authors (De Baets et al., 2017; De Baets et al., 2019), but demographic information suggested a low probability of overlapping participants. One study each was conducted in the US (Bovet et al., 2016), Spain (Palomo-Toucedo et al., 2020), and Norway (Sætre & Eik, 2019). Six studies had primary authors from the field of rehabilitation (Bennett et al., 2021; De Baets et al., 2017; De Baets et al., 2019; Palmer et al., 2016; Palmer et al., 2019; Sætre & Eik, 2019). Other disciplines represented in the studies’ authors included genetics (Bovet et al., 2016; De Baets et al., 2017; De Baets et al., 2019), psychology (De Baets et al., 2017; De Baets et al., 2019; Friedner, 2020; Pezaro et al., 2020; Schmidt et al., 2015; Terry et al., 2015), rheumatology (Schmidt et al., 2015), podiatry (Palomo-Toucedo et al., 2020), nursing (Palomo-Toucedo et al., 2020; Pezaro et al., 2020), community medicine (Terry et al.,
Sample sizes ranged from four in a provider interview sample (Palmer et al., 2016) to 393 in a sample of free-text survey responses (Palmer et al., 2019). All studies used samples that included patients. Also, one study included patients and healthcare providers (Palmer et al., 2016), and another study used patients and their family members (Friedner, 2020). Data collection methods included individual in-person, telephone, or video conferencing interviews (Bennett et al., 2021; De Baets et al., 2017; De Baets et al., 2019; Friedner, 2020; Palmer et al., 2016; Palomo-Toucedo et al., 2020; Pezaro et al., 2020; Sætre & Eik, 2019; Schmidt et al., 2015), synchronous text-message interviews (Pezaro et al., 2020), focus groups (Bovet et al., 2016; Palmer et al., 2016; Terry et al., 2015), and free-text responses to open-ended survey questions (Clark, 2012; Palmer et al., 2019). One study was a case analysis of a single family that used both individual and family group interviews (Friedner, 2020).

Six studies showed a diagnosis-related theme or subtheme, including (a) "Getting a diagnosis is a relief and supports the choice to become a mother" (De Baets et al., 2017, p. 138), (b) "The diagnosis" (De Baets et al., 2019, p. 4), (c) "JHS as a difficult to diagnose, chronic condition" (Palmer et al., 2016, p. 10), (d) "Impacts of living with JHS: Diagnosis" (Palmer et al., 2019, p. 186), (e) "The need to name the problem: the diagnosis" (Palomo-Toucedo et al., 2020, p. 1), and (f) "Receiving a diagnosis" (Terry et al., 2015, p. 356). In the remaining studies, the diagnosis was discussed within the context of other themes or subthemes.
Table 2.2

Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Location</th>
<th>Study type</th>
<th>Methodology</th>
<th>Sample</th>
<th>Recruitment</th>
<th>Findings re: Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett et al., (2021)</td>
<td>UK</td>
<td>Qualitative</td>
<td>Inductive thematic analysis; semi-structured telephone interviews</td>
<td>• Purposive • N = 17 (14 female, age not stated)</td>
<td>JHS/EDS-HT social media and online support groups; local NHS Trust</td>
<td>• Providers lack awareness of JHS/EDS-HT • Patients wait many years to get diagnosed • Providers may attribute symptoms to a mental health issue • Patients feel judged because their illness is &quot;invisible&quot;</td>
</tr>
<tr>
<td>Bovet et al., (2016)</td>
<td>US</td>
<td>Mixed methods</td>
<td>Framework approach; focus groups</td>
<td>• Convenience • N = 13 (10 female, age 28-57)</td>
<td>Medical genetics clinic, local support group, EDS-HT/JHS physical therapy program</td>
<td>• Poor communication and lack of provider knowledge lead to delayed diagnosis and iatrogenic injuries • Cost of visits, distance and time to tertiary care centers and long wait to see specialists may delay diagnosis • Providers may be dismissive and incredulous about patients' symptoms • Healthcare systems lack multidisciplinary coordination</td>
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<tr>
<td>Author (year)</td>
<td>Location</td>
<td>Study type</td>
<td>Methodology</td>
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<td>Clark, (2012)</td>
<td>UK</td>
<td>Mixed methods</td>
<td>Content analysis; free-text responses to open-ended questionnaire items</td>
<td>• Purposive</td>
<td>Hypermobility clinic</td>
<td>• Diagnosis may follow diagnosis of a family member • Providers lack awareness of the global nature of JHS • Providers may attribute patient's symptoms as a mental health issue • Healthcare systems are not designed to deal with a patient holistically</td>
</tr>
<tr>
<td>De Baets et al., (2019)</td>
<td>Belgium</td>
<td>Qualitative</td>
<td>Inductive thematic analysis; in-person, semi-structured interviews</td>
<td>• Purposive</td>
<td>National EDS association - Belgium</td>
<td>• Patients had difficulty declaring work incapacity because providers felt they were physically able to work • Patients experienced long delays and other diagnoses such as fibromyalgia before being diagnosed with hEDS</td>
</tr>
<tr>
<td>De Baets et al., (2017)</td>
<td>Belgium</td>
<td>Qualitative</td>
<td>Hermeneutical phenomenology; in-person or telephone semi-structured interviews</td>
<td>• Purposive</td>
<td>National EDS association - Belgium</td>
<td>• Diagnosis led to patients feeling relieved and understood and led to fewer doctor's visits • Patients feel misunderstood because the condition is &quot;invisible&quot;</td>
</tr>
<tr>
<td>Author (year)</td>
<td>Location</td>
<td>Study type</td>
<td>Methodology</td>
<td>Sample</td>
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<td>Findings re: Diagnosis</td>
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<tr>
<td>Friedner, (2020)</td>
<td>UK</td>
<td>Qualitative</td>
<td>Narrative framework; single family case study</td>
<td>• Purposive • N = 5 (single family, 2 adults, 3 children ages 12-17)</td>
<td>Adolescent medical service - UK</td>
<td>• EDS may be diagnosed as chronic fatigue, IBS, and/or chronic pain • EDS has no medical test to confirm the condition • Healthcare providers lack understanding of the condition • Patient diagnosis may be prompted by diagnosis of a family member</td>
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<tr>
<td>Palmer et al., (2019)</td>
<td>UK</td>
<td>Qualitative</td>
<td>Thematic analysis; free-text responses to open-ended questionnaire items</td>
<td>• Purposive • N = 393 (373 female, mean age 41)</td>
<td>National hypermobility association - UK.</td>
<td>• Diagnosis of JHS is a long process • Diagnosis facilitates self-management • Patients may feel misunderstood and mistreated by providers • Symptoms are unpredictable and invisible</td>
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<tr>
<td>Palmer et al., (2016)</td>
<td>UK</td>
<td>Mixed methods/ feasibility study</td>
<td>Thematic analysis; focus groups; individual interviews</td>
<td>• Purposive <strong>STAGE 1:</strong> Patients • N = 25 (22 female, age 19-60) <strong>Providers</strong></td>
<td>National hypermobility association - UK; health professionals and patients affiliated with</td>
<td>• Emotional responses to symptoms can lead to catastrophising • Providers may view patients as &quot;difficult&quot; due to their &quot;psychological baggage&quot; • JHS is not always recognized</td>
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<tr>
<td>Author</td>
<td>Location</td>
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<tr>
<td>Palomo-Toucedo et al., (2020)</td>
<td>Spain</td>
<td>Qualitative</td>
<td>Thematic analysis; semi-structured interviews</td>
<td>• Purposive</td>
<td>National EDS and hypermobility associations - Spain</td>
<td>• Pain and fatigue are the most problematic symptoms</td>
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<td>• N = 26 (21 female, age 18-57)</td>
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<td>• Symptoms impact patient psychological well-being</td>
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<td>• EDS is an &quot;invisible&quot; condition</td>
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<td>• Patients may be viewed as hypochondriacs</td>
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<td>• Diagnoses may be attached to individual symptoms</td>
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<td>• Economic factors may influence patient access to healthcare</td>
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<td>physiotherapy services at two NHS Trusts</td>
<td>• Providers lack knowledge about JHS</td>
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<td>• JHS does not fit the medical model of acute injury and recovery</td>
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<td>• JHS diagnostic criteria is difficult to use</td>
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<td></td>
<td>• Receiving the diagnosis is essential to access appropriate treatment</td>
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</tbody>
</table>

**STAGE 2:**
- **Patients**: N = 6 (6 female, age 22-41)
- **Providers**: N = 4

**STAGE 3:**
- **Patients**: N = 18 (15 female, age 18-66)
- **Providers**: N = 7

- JHS does not fit the medical model of acute injury and recovery
- JHS diagnostic criteria is difficult to use
- Receiving the diagnosis is essential to access appropriate treatment
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Location</th>
<th>Study type</th>
<th>Methodology</th>
<th>Sample</th>
<th>Recruitment</th>
<th>Findings re: Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pezaro et al., (2020)</td>
<td>UK</td>
<td>Qualitative</td>
<td>Thematic narrative analysis, social constructivism framework; telephone (n = 3) and synchronous text-message interviews (n = 37)</td>
<td>Purposive N = 40 (40 female, age 25-55)</td>
<td>EDS and hypermobility social media sites</td>
<td>• Increasing symptoms during pregnancy can lead to depression and anxiety&lt;br&gt;• Some healthcare providers have no knowledge of EDS&lt;br&gt;• Some healthcare providers have outdated or incorrect knowledge&lt;br&gt;• EDS patients may experience poor regional anesthetic response</td>
</tr>
<tr>
<td>Sætre &amp; Eik, (2019)</td>
<td>Norway</td>
<td>Qualitative</td>
<td>Phenomenology; thematic analysis; semi-structured in-person interviews</td>
<td>Purposive N = 7 (6 female, age 18-50)</td>
<td>Rehabilitation clinic</td>
<td>• Pain and fatigue are common features of JHS/EDS-HT&lt;br&gt;• JHS/EDS-HT is invisible to others&lt;br&gt;• Providers lack knowledge of JHS/EDS-HT</td>
</tr>
<tr>
<td>Schmidt et al., (2015)</td>
<td>UK</td>
<td>Qualitative</td>
<td>Interpretative phenomenology analysis; semi-structured in-person interviews</td>
<td>Purposive N = 11 (11 female, age 22-55)</td>
<td>Rheumatologist's referrals to a pain clinic</td>
<td>• Pain in JHS is unpredictable&lt;br&gt;• JHS can cause pain, anxiety, and catastrophizing&lt;br&gt;• Patients can experience emotional reactions including anger, depression, and guilt&lt;br&gt;• Patients may direct their frustration at diagnosis delays</td>
</tr>
<tr>
<td>Author (year)</td>
<td>Location</td>
<td>Study type</td>
<td>Methodology</td>
<td>Sample</td>
<td>Recruitment</td>
<td>Findings re: Diagnosis</td>
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</table>
| Terry et al., (2015) | UK | Qualitative | Inductive thematic analysis; focus groups | • Purposive  
• N = 25 (22 female, age 19-66) | National hypermobility association - UK; 2 NHS physiotherapy services | • Pain and recurrent injuries can lead to anxiety and catastrophizing  
• JHS is poorly understood by health professionals  
• Diagnosis delays result from being treated for individual symptoms, rather than as a whole  
• Diagnosis is necessary to access appropriate care pathways  
• Some providers do not believe JHS is a valid diagnosis |

*Notes. EDS, Ehlers-Danlos syndrome; EDS-HT, Ehlers-Danlos syndrome, hypermobility type; JHS, joint hypermobility syndrome; NHS, National Health Service*
Themes

We synthesized our findings into themes under disease, patient, provider, and system factors, as illustrated in Figure 2.2. Disease factors included the nature of the symptoms and no confirmatory test. Patient factors included psychological and emotional responses and multiple providers - multiple diagnoses. Provider factors included limited knowledge and negative attitudes. System factors included silo-based healthcare organizations and bureaucratic barriers. In these results, we discuss each factor and its associated themes.

Figure 2.2

Factors and Themes for Diagnosis Delay in hEDS/HSD
**Disease Factors**

**Nature of the Symptoms.** The included studies described a variety of symptoms experienced by patients with hEDS/HSD, including recurring joint dislocations and subluxations (Bennett et al., 2021; Bovet et al., 2016; Clark, 2012; De Baets et al., 2019; Palmer et al., 2016; Palmer et al., 2019; Palomo-Toucedo et al., 2020; Pezaro et al., 2020; Schmidt et al., 2015; Terry et al., 2015). poor proprioception (Clark, 2012; Palmer et al., 2016; Terry et al., 2015), poor sleep (Palmer et al., 2016; Palmer et al., 2019; Palomo-Toucedo et al., 2020; Pezaro et al., 2020; Sætre & Eik, 2019; Terry et al., 2015), local and regional anesthetic ineffectiveness (Bennett et al., 2021; Clark, 2012; Palmer et al., 2016; Pezaro et al., 2020), autonomic dysfunction (Bennett et al., 2021; Clark, 2012; Palmer et al., 2019; Pezaro et al., 2020), gastrointestinal disturbances (Bennett et al., 2021; Clark, 2012; Friedner, 2020; Palmer et al., 2016; Pezaro et al., 2020), migraines and headaches (Clark, 2012; Palmer et al., 2019; Pezaro et al., 2020), erectile dysfunction, and pelvic organ prolapse (Bennett et al., 2021). The most common and troublesome symptoms noted in all studies were chronic, widespread pain and fatigue. Episodic musculoskeletal pain begins early in life, often in adolescence, and may be associated with athletic activity or trauma (Clark, 2012). However, as the person ages, the pain becomes widespread and chronic. Participants described the pain as ever-present, stating, "it's always there, it never actually goes" (Palmer et al., 2016, p. 12). People with hEDS/HSD experience cycles of injury and recovery, which can complicate a person's evaluation of pain. According to one patient, "Well, how do we know whether we've injured something, because we've got pain all the time?" (Palmer et al., 2016, p. 11).
Fatigue may be more debilitating than pain, limiting daily routines and forcing daily life restructuring. As one participant described it, "Fatigue is much worse than pain, fatigue conditions a lot of things" (Palomo-Toucedo et al., 2020, p.5). Another stated, "it's not a fatigue you can sleep off" (Palmer et al., 2019, p.187). Other participants recognized the complex interplay between pain and fatigue and its impact on functioning, as described by one patient, "it’s a lot of pain, it’s a dull ache and it makes you sleepy and it makes you tired and you’re exhausted" (Palmer et al., 2016, p. 12).

The symptoms of hEDS/HSD are complex, fluctuating, unpredictable, and vary widely between individuals. Palmer et al. (2016) pointed out how the symptoms were diverse, and the impact and consequences varied between people. Also, the symptoms may vary from day to day in the same individual. As one participant observed, "I don't know how I'm going to be in two or three days" (Schmidt et al., 2015, p.162). In addition, the multisystemic nature of hEDS/HSD makes it challenging for patients and providers to make sense of the symptoms, with one patient admitting it was "hard to tell what illness is causing a problem" (Palmer et al., 2019, p.187).

No Confirmatory Test. Currently, there is no laboratory biomarker for hEDS/HSD. Participants note that hEDS/HSD is an invisible disorder in that the most debilitating symptoms, pain and fatigue, are not outwardly apparent, leading to skepticism and judgment from others (Bennett et al., 2021; Palomo-Toucedo et al., 2020). Participants stated, "I have sometimes thought that it would be better to have an amputated leg, so that people could see that I'm struggling" (De Baets et al., 2017, p. 139); "I look exactly the same as everyone else…I just don't have anything to show that I'm ill" (Friedner, 2020, p. 65); and, "no one would say at first sight that I have a chronic
disease, but of course I can't prove that" (Palomo-Toucedo et al., 2020, p. 6). This lack of a biomarker is problematic if patients undergo many clinical tests and become frustrated when results "come back fine" (Palmer et al., 2016, p. 80). This combination of vague, invisible symptoms and lack of confirmatory tests translates into lengthy diagnosis delays in hEDS/HSD.

**Patient Factors**

**Psychological and Emotional Responses.** All studies described hEDS/HSD's impact on participants' emotional and psychological well-being. As one participant described it, "My constant pain makes me irritable and low" (Clark, 2012, p. 165). Study participants also told how hEDS/HSD symptoms led to fear of the future, feeling like they are "in a constant state of anxiety" (Palmer et al., 2016, p. 13). One patient described the cycle of fear and catastrophizing about future deterioration: “Sometimes when you hurt a lot you are scared that it won't go away…. I was so scared I was going to be like that, that was going to be it “(Schmidt et al., 2015, p. 161). Some participants described a sense of hopelessness. According to one participant, “Clearly, one thinks about how one is going to end up and how mobile one will eventually be. I don't want to use a wheelchair…. It's so scary” (Sætre & Eik, 2019, p. 5).

Other participants felt guilt about their inability to manage daily tasks and their dependency on others. One male participant stated, "Sometimes I feel a burden, or a nuisance… that's why I end up… having the anxiety problems… feeling sorry for other people, having to put up with me" (Bennett et al., 2021, pp. 797-798). One provider-participant who was a physiotherapist acknowledged the challenges of treating hEDS/HSD patients:
For me they come with quite a lot of psychological baggage…they are difficult
patients…. they’re desperate to get help so the psychological side comes out
because the physical manifestation of what they're suffering with is just so severe
(Palmer et al., 2016, p. 15)

One participant described the interplay between anger and grief due to pain and activity
limitations, "you get angry, you get very angry, like you can't do this. It's like a
bereavement, it's like I've lost someone" (Schmidt et al., 2015, p. 163). In some cases,
patient anger is directed internally, as one participant stated, "I'm not doing my role as a
mother" (Schmidt et al., 2015, p. 163). Others directed their ire toward their healthcare
providers:

Feel very frustrated and angry about lack of awareness about JHS…. I have no
physical or mental energy left because of constant stress because of what people
have put me through because they know nothing about JHS (Clark, 2012, p. 164).

Anger and frustration with providers can lead people with hEDS/HSD to avoid healthcare
encounters. One participant noted, "unless its desperate I won't bother" (Bennett et al.,
2021, p.798). Another participant "withdrew from consultant's care…the consultant
would not listen" (Pezaro et al., 2020, p. 7).

**Multiple Providers-Multiple Diagnoses.** Patients with hEDS/HSD experience
many individual symptoms over time, and a possible connection between them may only
be appreciated after the fact. As a result, patients may have multiple healthcare
encounters and receive multiple diagnoses, including postural orthostatic tachycardia
syndrome (Clark, 2012; Palmer et al., 2019; Pezaro et al., 2020), irritable bowel
syndrome (Clark, 2012; Pezaro et al., 2020), fibromyalgia (Bennett et al., 2021; Clark,
De Baets et al., 2019; Palmer et al., 2019; Pezaro et al., 2020), chronic fatigue syndrome/myalgic encephalopathy (Clark, 2012; Pezaro et al., 2020), and spinal pathologies (Palmer et al., 2019; Pezaro et al., 2020). Palomo-Toucedo et al. (2020) stated, "In some cases, they spend many years until a diagnostic label is assigned to all the symptomology…they accumulate a number of diagnoses specific to each symptom" (p. 5). A physiotherapist described the complexity of working with patients who "had been treated in lots of different places and all been told lots of different things" (Palmer et al., 2016, p. 44). However, in some cases, investigation of another illness eventually led to the hEDS/HSD diagnosis. For example, one participant stated, "My hypermobility has been identified as a result of investigations into my chronic IBS" (Clark, 2012, p. 162).

**Provider Factors**

**Limited Provider Knowledge.** All included studies attributed delayed diagnoses to the lack of provider knowledge. Some providers had no familiarity with hEDS/HSD or any hypermobility or Ehlers-Danlos disorders, with one participant recalling their surgeon saying, "'What's Ehlers-Danlos?'" (Bennett et al., 2021, p. 798). One mother recalled how during her labor and delivery, "Nobody in the maternity unit had ever heard of EDS so did not know how to manage it" (Pezaro et al., 2020, p. 3). Other providers had limited, outdated, or incorrect understanding of the condition. Participants remembered their clinicians saying such things as, "hypermobility shouldn't be causing pain, it's just the way you are" (Palmer et al., 2016, p. 13), "you're not hypermobile because you can't touch the floor" (Pezaro et al., 2020, p. 3), and, "'ooh the stretchy skin thing'" (Pezaro et al., 2020, p. 7). Many providers did not know that chronic widespread pain was a common hEDS/HSD characteristic, believing it was a benign condition with
lax joints in otherwise healthy people: "hypermobility doesn’t cause pain" (Palmer et al., 2016, p. 14). Also, there are few knowledgeable specialists to whom patients with suspected hEDS/HSD can be referred. One health professional said, "there's no rheumatologist in the trust that has a special interest in hypermobility, and my god I've tried to find one" (Palmer et al., 2016, p. 15). According to another participant, "local doctors and rheum [sic] don't understand the problems" (Palmer et al., 2019, p. 189). So, when clinicians acknowledge their limited understanding and seek assistance with patients who may have hEDS/HSD, the specialty referral options are limited or unclear.

**Provider Attitudes.** Overall, participants reported problematic provider attitudes ranging from insensitivity and lack of empathy to accusing patients of fabricating illness. Some participants felt objectified by clinician statements such as, "Wow! You're such a freakshow!... let's get all the medical students here and show them!" (Bennett et al., 2021, p. 798). Patients also felt their clinicians dismissed their symptoms as unimportant or non-existent, with providers saying, "this is just EDS…there's nothing wrong with you" (Friedner, 2020, p. 98). Other participants were called hypochondriacs or experienced accusations of "making it up" (Bennett et al., 2021, p. 798). One participant stated, "she [consultant] would tell me… that I was making up my diagnosis of EDS" (Pezaro et al., 2020, p. 7). A few participants reported particularly egregious behavior from providers. For example, two participants who were unresponsive to local anesthetics told how providers refused to believe they could still feel pain during a procedure: "I could feel what they were doing. And I- I spoke up, and (. ) [the doctor] basically said, ‘No, you can’t.’ and… carried on" (Bennett et al., 2021, p. 798). Another stated, “I can still vividly
remember the feeling of the thread [suturing] being pulled through my skin" (Pezaro et al., 2020, p. 8).

According to most study participants, some clinicians believed hEDS/HSD was a psychiatric rather than a medical condition. As one provider stated, "I work in a rheumatology department who don't recognise joint hypermobility as an entity" (Palmer et al., 2016, p. 14). One patient said, "all this time I've been going to the doctors and being told that it's all in my mind" (Palmer et al., 2016, p. 80). And, according to another, "There are people who don't feel it's a genuine diagnosis, that it's something psychological" (Terry et al., 2015, p. 357).

**System Factors**

**Silo-based Healthcare System.** Despite efforts to advance patient-centered care and communication in healthcare organizations, specialties continue to operate in isolated "silos," separated according to discipline, body system, or function. Conditions with multisystemic impact add clinical complexity to primary care encounters and frequently lead to referrals to multiple specialists. As a result, patients feel their clinical care is fragmented and focused on individual body parts rather than their illness as a whole. As Clark (2012) stated, "the narrow focus of specialties may prevent health professionals from understanding the complex overlapping nature of multiple symptoms" (p. 188). According to one patient, "I was originally seen by a physio[therapist] … and then went back to a musculoskeletal specialist who then put me forward to specialist hypermobility physiotherapist" (Palmer et al., 2016, p. 16). Another said:

My 'journey' has highlighted how dis-jointed the approach to pelvis/back & joint problems is…There is a desperate need for a more holistic approach where
practitioners are willing (open to the idea) of secondary problems – looking at the body as a whole rather than in isolation (Clark, 2012, p. 188)

Another participant stated, "we’ve all been passed from pillar to post where people don’t recognise it or they just attribute a pain to something else, when a snap kind of diagnosis just comes out of the air" (Terry et al., 2015, p. 356). Participants expressed the need for a more patient-centered, holistic approach to complex, multisystemic conditions like hEDS/HSD: "Yeah, it's got to be holistic, it really has to be" (Terry et al., 2015, p. 357).

**Bureaucratic Barriers.** All healthcare systems suffer from bureaucratic issues that may delay or hamper diagnosis. Time, cost of visits, and long waits for specialty appointments may limit a patient’s access to healthcare (Bovet et al., 2016; Clark, 2012). According to one researcher, healthcare resource availability may depend on socioeconomic status, and "these are not accessible to everybody, so there is inequality" (Palomo-Toucedo et al., 2020, p. 8). According to one participant, “I would love to go [to physiotherapy], but I can’t afford it” (Palomo-Toucedo et al., 2020, p. 8). Another participant from the UK stated, "I have been suffering this problem for 9 yrs and have spent in excess of £10000 trying to find a solution" (Clark, 2012, p. 175).

Other bureaucratic barriers stemmed from organizations' demand for adherence to overly standardized and cumbersome clinical protocols. Strict protocols leave little flexibility for providers to take a holistic or creative approach or deviate from established care pathways. In some cases, this requirement can lead to poor outcomes in people with hEDS/HSD. For instance, thirty-eight percent of participants in Bovet et al. (2016) reported iatrogenic injuries from rehabilitation care, including hyperextensions, torn ligaments, and dislocations, which the researchers attributed to "physical therapists and
other providers who adhered to standard treatment protocols without adjusting for patients' specific needs" (p. 2047).

According to one participant:

they have a sort of, 'you're here for one joint' approach, which is quite difficult, because you go: 'Well, I'm floopy all over’… 'Well, which is the most difficult?' You're like 'Well, it's kind of all related' (Palmer et al., 2016, p. 16)

Other participants stated the problem was a lack of defined pathways for diagnosis or treatment of rare diseases or heritable disorders of connective tissue like hEDS/HSD. As one health care provider pointed out, "I think we don't have a structured pathway of care for hypermobiles" (Palmer et al., 2016, p. 15)

**Discussion**

**Summary**

The factors that contribute to hEDS/HSD diagnostic delays overlap and interact. The disease symptoms set into motion a series of actions and reactions among patients, providers, and systems that ultimately impact future symptoms and health outcomes. Multisystem, heterogeneous, and unpredictable symptoms in a little-known condition with no confirmatory test are challenging in primary care. The symptoms most likely to raise the suspicion of a connective tissue disorder are not usually the symptoms that drive patients to primary care providers. Musculoskeletal injuries like joint dislocations, particularly if recurrent, might lead a provider to consider a connective tissue dysfunction. However, these acute injuries are usually encountered in the emergency department or an orthopedic specialty clinic, where chronic pain, fatigue, and other multisystem problems are not likely to be evaluated. When hEDS/HSD patients fail to
respond to local or regional anesthetics, this is often discovered during dental procedures and not likely to be discussed in a primary care encounter. Multisystem symptoms, the most prominent of which are pain and fatigue, are likely attributed to conditions more familiar to primary care providers, such as fibromyalgia or chronic fatigue syndrome.

These symptoms also increase the likelihood that hEDS/HSD patients will be diagnosed with a psychiatric disorder (Cederlöf et al., 2016). Research has demonstrated a complex association between hEDS/HSD and psychiatric symptoms, including anxiety and depression, which may increase or prolong pain (Bulbena et al., 2017). Living with a chronic disease can cause a patient to feel anxious and depressed. Physiologic dysfunction such as dysautonomia can cause anxiety-like symptoms (Tinkle et al., 2017). Poor coping strategies may lead to kinesiophobia and alcohol and tobacco misuse (Bulbena et al., 2017). Clinicians may view patient behaviors, including catastrophizing, "doctor shopping," focusing excessively on minute details of symptoms, or fear-avoidance behaviors, as indicators of psychiatric pathology (Bennett et al., 2021; Kliegman et al., 2017). Unpredictable, invisible symptoms may cause a patient to be frustrated and angry and may set up an adversarial dynamic in the patient-provider relationship. A poor patient-provider relationship may lead patients to avoid healthcare encounters, thereby prolonging the diagnosis delay.

The lack of a biomarker, unremarkable symptoms, and limited provider awareness about hEDS/HSD can lead to care fragmentation and diagnosis delay (Kalisch et al., 2019). Providers' knowledge of the disorder depends on differences in educational background, clinical discipline, and the rapidly evolving understanding of hEDS/HSD in light of new research. Primary care providers may lack the knowledge, expertise, or time
to evaluate their patients according to the 2017 diagnostic criteria and opt for specialist referral to make a diagnosis. However, it may be unclear who is appropriate or available for an hEDS/HSD referral, as this depends on the clinical practice, location, payer source, and healthcare organization. There is no consensus in the medical field regarding which specialty should diagnose and treat hEDS/HSD. Consequently, hEDS/HSD patients undergo multiple specialty referrals and accumulate multiple diagnoses before a connective tissue disorder is suspected. These multiple diagnoses accumulate and follow the patient from provider to provider. Once a diagnosis is included in a medical record, it is assumed to be correct and rarely questioned or revisited making early, potentially incorrect diagnoses perpetuate over time (Kliegman et al., 2017). Also, the sheer volume and duplication of data in the electronic health record make it difficult to identify trends, thereby obscuring the picture of a possible unifying etiology such as a connective tissue disorder (Barwise et al., 2021). Organizations and policymakers must look at communication avenues between researchers, specialists, and primary care providers and explore ways to facilitate critical patient information sharing in the context of the varied, changing, and sometimes chaotic healthcare system landscape.

**Strengths and Limitations**

The primary strength of this study is its consistent findings across multiple countries and healthcare specialties. However, this review has limitations. Provider factors were extrapolated from patients' statements, as there were few providers in the study samples. The search for and retrieval of unpublished dissertations for inclusion helped mitigate publication bias; however, we may have missed pertinent articles in the search process. In addition, this study reviewed only the published version of the articles;
the original raw data may contain additional diagnosis information. Because there is little qualitative research on the topic, these findings may not reflect others' perspectives of the diagnosis experience with hEDS/HSD. Most study participants were female. Although symptomatic adult females outnumber males with hEDS/HSD, future research highlighting men's diagnosis trajectory may provide important information and perspective about the diagnosis barriers in the population as a whole. System barriers may vary due to the healthcare structures in different countries. The complexity of these issues suggests opportunities for collaborative cross-disciplinary and systems research.

Conclusion

To our knowledge, this is the first qualitative review about the complex, multifaceted reasons for diagnosis delay in hEDS/HSD. As such, there are implications for both practice and research. No article specifically aimed to uncover reasons for diagnosis delays; however, the findings were consistent across all studies. This review demonstrates the need for further research to deepen our understanding of the multiple, complex factors that contribute to delayed and missed diagnosis of hEDS/HSD.
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Chapter Three

Clinical Trajectory of Hypermobile Ehlers-Danlos Syndrome/Hypermobility Spectrum Disorders in Older Adults: A Scoping Review


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**Authorship Statement**

Linda K. Anderson performed the topic selection and development, literature search, study selection, results synthesis, and drafted the initial manuscript. Kari R. Lane assisted in study selection and results synthesis and critically reviewed the manuscript for important intellectual content. Both authors approved the final manuscript for publication.
Abstract

**Background.** Research on hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders (hEDS/HSD) has described its natural history and clinical course in children, adolescents, and young to middle-aged adults. However, there needs to be more research on the clinical trajectory of hEDS/HSD into older age. Therefore, clinicians, including nurse practitioners, know little about identifying older adults with undiagnosed hEDS/HSD. **Objective.** This review sought to identify studies regarding aging in hEDS/HSD. **Data Sources.** This scoping review searched PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Scopus and found fifteen studies that mentioned age or aging on the symptoms and health-related quality of life. **Conclusions.** No study had a stated aim regarding aging in hEDS/HSD, but all studies corroborated earlier natural history studies describing the age-related trajectory of manifestations in younger people. Studies found that symptom progression was heterogeneous, multisystemic, and unpredictable. Studies also noted prolonged diagnosis delays and long symptom duration, but the impact of these factors on outcomes was unclear. The high variability in patient outcomes precludes the prediction of outcomes based on the included studies. The clinical impact of aging on hEDS/HSD remains mostly speculative. **Implications for Practice.** Nurse practitioners, especially those in primary care, should consider that older adults presenting with multimorbidity may have undiagnosed hEDS/HSD. More research is needed to identify symptom patterns and clinical history that may suggest an underlying connective tissue disorder.

**Keywords:** aging; Ehlers-Danlos syndrome; joint hypermobility; quality of life; symptom assessment
Clinical Trajectory of Hypermobile Ehlers-Danlos Syndrome/Hypermobility Spectrum Disorders in Older Adults: A Scoping Review

Hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders (hEDS/HSD) describe a classification of inherited connective tissue disorders characterized by joint instability, tissue fragility, chronic pain, and progressive multisystem dysfunction (Castori et al., 2017; Tinkle et al., 2017). The precise genetic basis of hEDS/HSD remains elusive, and diagnosis is based on clinical features (Malfait et al., 2017). The defining feature of hEDS/HSD is current or historic joint hypermobility, or the ability to move a joint past its normal limits (Juul-Kristensen et al., 2017). Researchers previously believed hEDS/HSD was rare, affecting approximately one in 5000 people worldwide, but a 2019 study from Wales placed the combined hEDS/HSD prevalence at one in 500 (Demmler et al., 2019). Without a definitive biomarker for diagnosis and clinicians’ limited understanding of hEDS/HSD, researchers believe prevalence estimates are low due to underdiagnosis (Demmler et al., 2019).

Current research suggests hEDS/HSD transmits in an autosomal dominant fashion, with more symptomatic adult females than males indicating a possible hormonal influence on phenotypic expression (Castori et al., 2010b).

Research suggests that hEDS/HSD, like other EDS types, alters the collagen fibers and extracellular matrix of the connective tissues responsible for joint, blood vessel, skin, and organ system integrity (Chiarelli et al., 2019). Normal age-related changes in collagen properties and content impact connective tissue, leading to systemic changes over time, manifesting as skin aging, osteoarthritis, and osteoporosis (Sarbacher & Halper, 2019). Because connective tissue is present throughout the body, changes over...
time can lead to multisystemic, non-specific, and unpredictable symptoms influenced by age, gender, and lifestyle (Castori et al., 2017; Tinkle et al., 2017). Natural history studies of hEDS/HSD show progressive joint dysfunction and increasing pain, fatigue, and multisystemic problems from childhood through adulthood, ultimately leading to functional disability and poor health-related quality of life (HRQOL; Berglund et al., 2015; Castori et al., 2010a, 2011).

However, because earlier studies used relatively young samples, no study has specifically examined growing older with hEDS/HSD. Thus, clinicians need guidance regarding symptom patterns that would aid in recognizing the condition in undiagnosed older adults. A diagnosis facilitates establishing an effective treatment plan and enables coordination with other disciplines to optimize clinical outcomes. In the absence of specific research regarding this condition in older adults, this scoping review aims to answer the question: What research is available that discusses the clinical trajectory or evolution of symptoms in the context of age or aging in adults with hEDS/HSD?

**Method**

**Study Design**

This review’s approach is broadly based on the methodological framework established by Arksey & O’Malley (2005). A scoping review is appropriate to examine the extent of research on a topic, identify gaps, and determine the value of undertaking an extensive systematic review (Arksey & O’Malley, 2005; Munn et al., 2018). This review is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR; Tricco et al., 2018).
**Eligibility Criteria**

This search sought original experimental, quasi-experimental, observational, or qualitative studies or case reports in adults aged 18 and over diagnosed with hEDS/HSD. The search included studies using the current and historical analogous terms for hEDS/HSD, including Ehlers-Danlos syndrome, hypermobility type (EDS-HT); Ehlers-Danlos, type III (EDS III); hypermobility syndrome; joint hypermobility syndrome (JHS); and benign joint hypermobility syndrome (BJHS). Studies were included if they reported an association between age and a health outcome or mentioned age or aging with hEDS/HSD. This study excluded editorials, reviews, consensus opinions, conference abstracts, pediatric studies, and studies that reported results on multiple EDS types with no subgroup analysis on hEDS/HSD. Articles were limited to the past ten years.

**Search Strategy**

A search was conducted for articles published between January 1, 2012, and October 1, 2022, in PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Scopus. The searches used medical subject headings (MeSH) and keywords on the title or abstract, combining primary search terms for hypermobile Ehlers-Danlos syndrome, hypermobility syndrome, symptom burden, disease burden, quality of life, aging, older adults, and evolving phenotype. In addition to database searches, eligible studies’ reference lists were reviewed, and select journals were hand-searched for additional pertinent articles. Figure 3.1 shows an example of the PubMed search terms.
Study Selection

Search results were downloaded into the online bibliographic service Zotero (https://www.zotero.org) for tracking and duplicate removal. After duplicate removal, the first author reviewed and excluded records that did not meet inclusion criteria based on title and abstract. The first author examined the remaining studies’ full text for inclusion, which the second author subsequently verified.

Figure 3.1

PubMed Search Strategy


Data Charting Process

A data extraction form was created, including author names, publication year, full citation, keywords, first author’s clinical discipline, country, purpose, design and method, sample and setting, outcome variables and measures, analysis methods, main findings,
findings specific to the research question, and study limitations. The first author independently performed the initial data extraction, which the second author subsequently reviewed and verified. The authors agreed on the article selection, data extraction, results, and analysis.

Results

Study Selection

Figure 3.2 shows the search strategy and study selection process. The initial database search retrieved 500 articles, with five additional articles added from the ancestry search. After removing 100 duplicates, 405 articles remained to screen. A total of 283 articles were excluded based on title or abstract, leaving 122 for full-text review. After a full-text review, 107 articles were excluded as not meeting inclusion/exclusion criteria (67 had no age-related outcome or discussion, 33 did not report results specific to hEDS/HSD, and seven were not research studies). Fifteen studies were included in this scoping review.

Study Characteristics

Table 3.1 shows the characteristics of the included studies. Six studies were conducted in the United States (Alomari et al., 2020; Bergl et al., 2019; Glayzer et al., 2021; Murray et al., 2013; Schubart et al., 2019, 2022), four in France (Baeza-Velasco et al., 2021; Bénistan & Martinez, 2019; Hugon-Roden et al., 2016; Kalisch et al., 2020), two in Belgium (Coussens et al., 2021; De Wandele et al., 2014), two in Italy (Castori et al., 2015; Puledda et al., 2015), and one in the Netherlands (Scheper et al., 2016). Two studies were retrospective reviews (Alomari et al., 2020; Schubart et al., 2019), two were longitudinal (Coussens et al., 2021; Schubart et al., 2022), and one each case-control
(Puledda et al., 2015), prospective case series (Bénistan & Martinez, 2019), and
individual case report (Bergl et al., 2019). The remaining eight studies were cross-
sectional. Eight studies used in-person clinical assessments or questionnaires (Baeza-
Velasco et al., 2021; Bénistan & Martinez, 2019; Castori et al., 2015; Coussens et al.,
2021; Hugon-Rodin et al., 2016; Kalisch et al., 2020; Puledda et al., 2015; Scheper et al.,
2016). Four studies used only postal or internet surveys (De Wandele et al., 2014;
Glayzer et al., 2021; Murray et al., 2013; Schubart et al., 2022). The remaining studies
extracted data from existing records (Alomari et al., 2020; Bergl et al., 2019; Schubart et
al., 2019).

The sample sizes ranged from one (Bergl et al., 2019) to 1,146 (Glayzer et al.,
2021). The sample mean ages ranged from 31.2 (Castori et al., 2015) to 57 (Bergl et al.,
2019). Omitting the Bergl et al. (2019) case study with one participant, the next oldest
mean sample age was 49 at the final assessment (Coussens et al., 2021). Several studies
had at least one author in common. Despite shared authors and possible shared
recruitment pools, no samples appeared identical. Because outcome measures differed
among these studies, any participant overlap was considered inconsequential for this
review. Four studies used comparison groups. Two studies compared individuals with
hEDS/HSD to healthy controls (Coussens et al., 2021; Scheper et al., 2016). One study
compared individuals with migraines and joint hypermobility syndrome (JHS) or Ehlers-
Danlos syndrome, hypermobility type (EDS-HT), to individuals with migraines but
without JHS/EDS-HT (Puledda et al., 2015). One study compared individuals with EDS-
HT to four groups: classical EDS, vascular EDS, fibromyalgia, and healthy controls (De
Wandele et al., 2014).
Figure 3.2

Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Flow Diagram

- Identification:
  - Records identified through database searching
    - (n = 500)
    - PubMed (n = 199)
    - CINAHL (n = 172)
    - Scopus (n = 129)
  - Additional records identified through other sources
    - (n = 5)

- Screening:
  - Duplicates removed
    - (n = 100)
  - Title/abstracts screened
    - (n = 405)
  - Records excluded on title/abstract
    - (n = 283)

- Eligibility:
  - Full-text articles assessed for eligibility
    - (n = 122)
  - Full-text articles excluded, with reasons
    - (n = 107)
    - Not specific to hEDS/HSD = 33
    - No age-related outcome = 67
    - Not a research study = 7

- Included:
  - Studies included in review
    - (n = 15)
<table>
<thead>
<tr>
<th>Author, year (Country)</th>
<th>Study Aim</th>
<th>Methodology</th>
<th>Sample</th>
<th>Recruitment</th>
<th>Findings re: Age/aging</th>
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</table>
| Alomari et al., 2020 (US) | Evaluate gut dysmotility prevalence and associated factors in hEDS patients | Retrospective record review | Convenience ($n = 218$, median age 32, 91% female) | Genetics clinic patients newly diagnosed with hEDS | • hEDS diagnosis median age 32  
• 62% of hEDS patients had a GI symptom at the time of diagnosis (commonly abdominal pain, nausea, and/or constipation)  
• 41% of hEDS patients with IBS were diagnosed with hEDS by age 30, 81.2% by age 50  
• Cumulative incidence of GI dysmotility in hEDS patients was 11% by age 30, 21% by age 50. |
| Baeza-Velasco et al., 2021 (France) | Understand suicidal behaviors and ideation in women with hEDS; explore factors associated with suicide attempts | Cross-sectional; in-person questionnaire and assessment | Convenience ($n = 35$, mean age 40, 100% female) | Participants in a previous study | • hEDS symptom onset mean age 15  
• hEDS diagnosis mean age 36  
• Diagnosis delay mean 20 years  
• hEDS patients with a history of suicide attempts were significantly younger (mean age 33) than hEDS patients without a history of suicide attempts (mean age 43) |
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<tr>
<th>Author, year (Country)</th>
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| Bénistan & Martinez, 2019 (France) | Describe pain and its neurophysiological aspects in hEDS | Prospective case series; in-person questionnaire and assessment | Convenience ($n = 37$, mean age 26, 95% female) | Consecutive hEDS patients at an EDS outpatient clinic | • hEDS diagnosis mean age 24  
• Pain onset mean age 10  
• Pain became chronic mean age 20  
• First dislocation/sprain mean age 10  
• Eight participants (22%) reported suicide attempts at young age, mean 18 |
| Bergl et al., 2019 (US) | Discuss diagnostic approach in a middle-aged female with undiagnosed hEDS and multiple comorbidities | Case report | 57-year-old female | Clinical outpatient | • Describes clinical history and symptom progression in hEDS in a middle-aged female  
• Dislocations since childhood; diffuse arthralgias since 20s; hx fatigue, frequent headaches, chronic GI symptoms, pelvic floor dysfunction, dysautonomia, easy bruising, family hx early onset arthritis |
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<tr>
<td>Castori et al., 2015 (Italy)</td>
<td>To delineate a comprehensive picture of the cutaneous and mucosal findings in JHS/EDS-HT</td>
<td>Cross-sectional; in-person assessment</td>
<td>Convenience • JHS/EDS-HT patients (n = 277, mean age 31, 83% female)</td>
<td>JHS/EDS-HT patients with cutaneous and mucosal features from a heritable connective tissue disorders clinic</td>
<td>• Inverse correlation between age and joint hypermobility by Beighton Score • Premature skin aging, striae, gingival recessions/inflammation, enamel discolorations, and resistance to local anesthetics tend to occur in older patients • Three general age-related phenotypic presentations: o 0-20 yrs: predominantly male; high BS; keratosis pilaris/hyperkeratosis of extensor surfaces o 21-30 years: both sexes; atrophic non-papyraceous scars, piezogenic papules, striae, perhaps blue sclera and hyperextensive skin o &gt; 30 yrs: predominantly female; lower BS, acquired cutis laxa/premature skin aging, sometimes abdominal hernias, gingival/mucosal fragility, and resistance to local anesthetics</td>
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<td>Author, year (Country)</td>
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| Coussens et al., 2021 (Belgium) | Investigate the evolution of muscle strength in hEDS/HSD | Longitudinal cohort; postal survey, in-person assessment; length of follow-up 8 years | Convenience  
  - hEDS/HSD group:  
    o T1 ($n = 43$, mean age 41);  
    o T2 ($n = 30$, mean age 49)  
  - Control group:  
    o T1 ($n = 43$, mean age 41);  
    o T2 ($n = 17$, mean age 49) | Participants in a previous study |  
  - Overall, hEDS/HSD group showed weaker muscle strength, more pain, and worse function than controls at baseline and follow-up  
  - Peak torque of the knee flexors declined in control group over time, but remained stable in hEDS/HSD group  
  - hEDS/HSD group more likely to receive PT regularly than control group (40% vs 0%)  
  - hEDS/HSD group more likely to exercise regularly than control group (33% vs 6%)  
  - hEDS/HSD group reported more injuries (57% vs 47%) and surgeries (56% vs 35%) over time than control group |
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| De Wandele et al., 2014 (Belgium) | Understand autonomic symptom profile and the impact on HRQOL in EDS-HT; and compare these autonomic symptoms to fibromyalgia, other EDS types, and healthy controls | Cross-sectional; email or postal survey | Convenience EDS groups \(n = 98\)  
  o EDS-HT \(n = 80\), mean age 41, 94% female  
  o cEDS \(n = 11\), mean age 32, 64% female  
  o vEDS \(n = 7\), mean age 37, 50% female  
  Fibromyalgia group \(n = 38\), mean age 48, 100% female  
  • Healthy control group \(n = 43\), mean age 38, 79% female | • EDS group recruited from a genetics clinic  
  • Fibromyalgia group recruited from PM&R clinic  
  • Healthy controls recruitment source not specified | • The orthostatic domain of the Autonomic Symptom Profile decreased slightly with age in the EDS-HT group |
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<tr>
<td>Glayzer et al., 2021 (US)</td>
<td>Determine rates of dyspareunia and vulvodynia and associated comorbidities in women with EDS/HSD</td>
<td>Cross-sectional; internet survey</td>
<td>Convenience • Women with EDS/HSD ($n = 1146$, mean age 38, 91% hEDS type; 100% female)</td>
<td>Social media</td>
<td>• Age had a nonlinear relationship with the odds of women with hEDS/HSD having dyspareunia; middle aged women had the lowest odds, while younger and older women had higher odds of having dyspareunia. • Age had a linear relationship with the odds of women with hEDS/HSD having vulvodynia, decreasing with each 1-year increase in age</td>
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<td>Hugon-Rodin et al., 2016 (France)</td>
<td>Describe obstetric and gynecologic history and symptoms in hEDS</td>
<td>Cross-sectional; in-person questionnaire and assessment</td>
<td>Convenience • Patients with hEDS ($n = 386$, mean age 38, 100% female)</td>
<td>Patients with hEDS referred to a gynecology service in France</td>
<td>• Menorrhagia reported by 76%; dysmenorrhea reported by 72.8%; frequencies did not differ by age • 70.4% women experienced hEDS symptom onset before puberty; of those, 52% reported hEDS symptoms worsened with puberty. • 22% of postmenopausal participants reported symptom improvement after menopause</td>
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| Kalisch et al., 2020 (France) | Identify factors that influence pain and mobility disability in hEDS | Cross-sectional; in-person questionnaire | Convenience • Patients with hEDS ($n=75$, mean age 36, 89% female) | EDS clinic in France | • Longer diagnosis delays were associated with greater odds of severe pain  
• Physical functioning decreased with age |
| Murray et al., 2013 (US) | Describe the experience of living with EDS-HT including the symptom and pain experience | Cross-sectional; internet survey | Convenience • Patients diagnosed with EDS-HT ($n=466$, 90% female) | Local and national EDS support groups and a genetics clinic in the US | • Most participants reported joint hypermobility and skin manifestations onset in childhood.  
• 79% of participants reported joint pain, dislocations, and subluxations onset before age 18  
• Participants with depression, anxiety, and chronic fatigue reported age of onset for these symptoms between 18 and 30. |
| Puledda et al., 2015 (Italy) | Describe prevalence, frequency and characteristics of migraine headaches in adults with JHS/EDS-HT | Prospective case control; internet survey, in-person assessment | Convenience • Cases: Patients with migraines and JHS/EDS-HT ($n=33$, mean age 32, 88% female)  
• Controls: Patients from a heritable connective tissue disorders clinic  
• Controls: Patients from a headache clinic | • Cases: Patients from a heritable connective tissue disorders clinic  
• Controls: Patients from a headache clinic | • Age of migraine onset is significantly younger in JHS/EDS-HT patients (mean age 12) than in non-JHS/EDS-HT patients (mean age 17) |
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<tr>
<td>Scheper et al., 2016 (The Netherlands)</td>
<td>Establish the association between muscle strength, activity limitations, and proprioception in EDS-HT patients</td>
<td>Cross-sectional; in-person questionnaire and assessment</td>
<td>Convenience - • Patients: EDS-HT patients ($n = 24$, mean age 41, 100% female) • Controls: Healthy volunteers ($n = 24$, mean age 39, 100% female)</td>
<td>Cases: Patients from a medical genetics clinic in the Netherlands Controls: Recruitment not specified</td>
<td>• Duration of pain mean 24 years • Duration of soft-tissue injuries mean 23 years • Increasing age was associated with greater activity limitations</td>
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<td>Author, year (Country)</td>
<td>Study Aim</td>
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<tr>
<td>Schubart et al., 2022 (US)</td>
<td>Examine symptom changes over time in patients with EDS</td>
<td>Longitudinal cohort; survey; length of follow-up median 12 years, range 5-16 years.</td>
<td>Convenience • EDS patients ($n = 91$, mean age 39, 75% female) • hEDS patient subset ($n = 21$ (23% of participants))</td>
<td>Participants in a previous study/registry for heritable connective tissue disorders</td>
<td>• Older age at baseline was associated with worse pain severity, pain interference, and sleep quality • Pain severity and pain interference worsened in hEDS patients over 10 years • Associations between age at baseline and time on outcomes, while significant, did not exceed minimal clinically important difference thresholds • Men had lower baseline pain severity but greater mean increase over time than women • High variability in within-participant outcomes limits the prognostic value of results for individual patients</td>
</tr>
<tr>
<td>Schubart et al., 2019 (US)</td>
<td>Identify phenotypic subgroups of Ehlers-Danlos syndrome patients</td>
<td>Retrospective registry review</td>
<td>Convenience • EDS patients ($n = 175$, mean age 42, 77% female) • hEDS subgroup ($n = 34$)</td>
<td>Participants in a previous study/registry for heritable connective tissue disorders</td>
<td>• 53% of hEDS patients were in the High Symptom Burden cluster which was associated with high mean values in all variables including pain, physical and mental fatigue, younger age, longer time since diagnosis, and greater disability</td>
</tr>
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</table>
Notes. BS, Beighton score; cEDS, classical Ehlers-Danlos syndrome; EDS, Ehlers-Danlos syndrome; EDS-HT, Ehlers-Danlos syndrome, hypermobility type; hEDS, hypermobile Ehlers-Danlos syndrome; HSD, hypermobility spectrum disorder; hx, history; IBS, irritable bowel syndrome; JHS, joint hypermobility syndrome; PM&R, physical medicine and rehabilitation; PT, physical therapy/physiotherapy; T1, timepoint 1; T2, timepoint 2
The sample sizes ranged from one (Bergl et al., 2019) to 1,146 (Glayzer et al., 2021). The sample mean ages ranged from 31.2 (Castori et al., 2015) to 57 (Bergl et al., 2019). Omitting the Bergl et al. (2019) case study with one participant, the next oldest mean sample age was 49 at the final assessment (Coussens et al., 2021). Several studies had at least one author in common. Despite shared authors and possible shared recruitment pools, no samples appeared identical. Because outcome measures differed among these studies, any participant overlap was considered inconsequential for this review. Four studies used comparison groups. Two studies compared individuals with hEDS/HSD to healthy controls (Coussens et al., 2021; Scheper et al., 2016). One study compared individuals with migraines and joint hypermobility syndrome (JHS) or Ehlers-Danlos syndrome, hypermobility type (EDS-HT), to individuals with migraines but without JHS/EDS-HT (Puledda et al., 2015). One study compared individuals with EDS-HT to four groups: classical EDS, vascular EDS, fibromyalgia, and healthy controls (De Wandele et al., 2014).

The study aims and outcomes varied widely. Two longitudinal studies examined physiologic function or symptom evolution over time (Coussens et al., 2021; Schubart et al., 2022). Other studies evaluated the prevalence of hEDS/HSD-associated symptoms or comorbidities, such as gut dysmotility (Alomari et al., 2020), mucocutaneous findings (Castori et al., 2015), autonomic symptoms (De Wandele et al., 2014), gynecologic symptoms (Glayzer et al., 2021; Hugon-Rodin et al., 2016), pain (Bénistan & Martinez, 2019; Kalisch et al., 2020; Murray et al., 2013), migraine headaches (Puledda et al., 2015), muscle strength (Scheper et al., 2016), and suicidal behaviors (Baeza-Velasco et al., 2021). One study used cluster analysis of registry data to delineate EDS phenotypic
subgroups (Schubart et al., 2019). The final study was a case report detailing the clinical reasoning and diagnostic approach with a middle-aged woman with undiagnosed hEDS/HSD.

**Symptom Evolution**

**Pain**

Pain was the most common symptom described in these studies. Most participants reported that pain began in childhood or adolescence (Baeza-Velasco et al., 2021; Bénistan & Martinez, 2019; Bergl et al., 2019; Hugon-Rodin et al., 2016; Murray et al., 2013). Participants characterized the pain as severe, chronic, and increasing over time (Baeza-Velasco et al., 2021; Bénistan & Martinez, 2019; Schubart et al., 2022). Most reported pain was musculoskeletal, primarily joint pain (Bénistan & Martinez, 2019; Coussens et al., 2021; Hugon-Rodin et al., 2016; Scheper et al., 2016; Schubart et al., 2019); however, abdominal pain (Alomari et al., 2020), migraine headaches (Puledda et al., 2015), and pelvic/vaginal pain (Glayzer et al., 2021; Hugon-Rodin et al., 2016) were also reported. Besides pain, severe, chronic fatigue was reported in many studies (Bénistan & Martinez, 2019; De Wandele et al., 2014; Hugon-Rodin et al., 2016; Kalisch et al., 2020; Scheper et al., 2016; Schubart et al., 2019, 2022). Diagnosis delays were common, ranging from 14 years (Bénistan & Martinez, 2019) to 22 years (Hugon-Rodin et al., 2016; Kalisch et al., 2020). Two studies suggested that pain severity may be influenced by diagnosis delays or disease duration (Bénistan & Martinez, 2019; Kalisch et al., 2020).

**Multisystemic Manifestations**
The earliest hEDS/HSD symptoms were reported as musculoskeletal in nature. Six studies found that musculoskeletal symptoms such as muscle weakness, joint dislocations/subluxations, and soft tissue injuries were common and tended to worsen over time, contributing to functional disability and poor quality of life (Bénistan & Martinez, 2019; Coussens et al., 2021; Hugon-Rodin et al., 2016; Kalisch et al., 2020; Murray et al., 2013; Scheper et al., 2016). However, in most participants, symptoms eventually became multisystemic and included cardiovascular and autonomic dysfunction (Alomari et al., 2020; De Wandele et al., 2014; Murray et al., 2013; Puledda et al., 2015); gastrointestinal symptoms including gut dysmotility, abdominal pain, gastroesophageal reflux disease, diarrhea, nausea, and constipation (Alomari et al., 2020; Bénistan & Martinez, 2019; De Wandele et al., 2014; Murray et al., 2013; Puledda et al., 2015; Scheper et al., 2016); skin and mucocutaneous symptoms (Bénistan & Martinez, 2019; Castori et al., 2015; Murray et al., 2013; Scheper et al., 2016); genitourinary difficulties (Alomari et al., 2020; Bénistan & Martinez, 2019; Glayzer et al., 2021; Hugon-Rodin et al., 2016; Murray et al., 2013; Puledda et al., 2015); sleep disturbances (Schubart et al., 2019; 2022); and neurological and psychological problems including headaches (Bénistan & Martinez, 2019; Hugon-Rodin et al., 2016; Murray et al., 2013; Puledda et al., 2015), depression and anxiety (Bénistan & Martinez, 2019; De Wandele et al., 2014; Murray et al., 2013; Puledda et al., 2015), and suicidal ideation (Bénistan & Martinez, 2019; Baeza-Velasco et al., 2021).

**Physical Function**

Three studies explored physical function in individuals with hEDS/HSD. Scheper et al. (2016) found that hypermobile participants had lower muscle strength than normal
controls and that muscle strength and age were significantly associated with activity limitations. Correspondingly, Kalisch et al. (2020) also found that physical function declined with age but noted that the maximum sample age was 58 and theorized that physical decline might be explained by longer disease duration rather than biological aging. Coussens et al. (2021) noted that people with hEDS/HSD had weaker muscle strength than people without hEDS/HSD at baseline and follow-up, yet maintained some strength of the knee flexors over time. The authors speculated that this finding might be due to a greater prevalence of regular physical therapy and exercise in the hEDS/HSD groups than in the control group.

Health-Related Quality of Life

Four studies assessed HRQOL. De Wandele et al. (2014) found autonomic symptoms were associated with lower HRQOL but found no association between age and HRQOL. Murray et al. (2013) found that 82% of respondents reported EDS-HT affected work or school performance, and 55% reported needing special accommodations to manage work or school. Schubart et al. (2022) found that the hypermobile type of EDS was associated with low Short Form 36 (SF-36) physical and mental component scores but reported no association between those scores and baseline age nor a 10-year increase in time. Schubart et al. (2019) defined three EDS symptom clusters and reported that the High Symptom Burden subgroup had lower HRQOL scores, was slightly younger and had overall greater disability than the other EDS subgroups. Although these studies found that hEDS/HSD was associated with poor HRQOL, the relationship between age and HRQOL in this population remains unclear.
Discussion

The findings from the included studies lend little clarity to the clinical presentation or symptom evolution in older adults with hEDS/HSD. Nevertheless, this scoping review corroborated earlier natural history studies describing the age-related trajectory of multisystemic manifestations in younger to middle-aged adults. A population-based survey in the U.K. by Mulvey et al. (2013) found that widespread chronic pain prevalence in the general population peaked at 19.2% in the sixth decade and decreased with age to 17.4% in ages ≥ 80. The Mulvey et al. study noted that people with joint hypermobility were more likely than people without joint hypermobility to report chronic widespread pain, 18.5% versus 15.8. However, consistent with Castori et al. (2010a, 201), the Mulvey et al. study also noted that joint hypermobility prevalence decreased with age, from 31.3% in ages 19 - 29 to 14.5% in ages ≥ 78. These results demonstrate the complexity of comparing older adults with chronic pain and asymptomatic hypermobility with older adults who have hEDS/HSD but may have lost joint hypermobility, pointing to the need for more research regarding the relationships among age, pain, and joint hypermobility.

The included studies suggest that symptom progression is neither linear nor predictable. For example, Glayzer et al. (2021) found that the odds of vulvodynia in women with hEDS/HSD decreased linearly with increased age. However, this same study found that middle-aged women with hEDS/HSD had lower odds of having dyspareunia than younger and older women. Hugon-Rodin et al. (2016) found that 22% of postmenopausal participants experienced symptom improvement after menopause. Coussens et al. (2021) demonstrated that muscle strength in hEDS/HSD might not
decrease over time as expected, particularly in people participating in regular physical therapy and exercise. Finally, De Wandele et al. (2014) reported lower autonomic symptom profile orthostatic domain scores with increased age. These results demonstrate a need for further research into symptom progression with age.

Diagnosis delays are frequent in hEDS/HSD due to complex disease, patient, provider, and system factors (Anderson & Lane, 2021; Halverson et al., 2021; Hamonet et al., 2017). Nevertheless, currently, no research shows that these diagnosis delays contribute to poor outcomes, nor whether outcomes are related to age, time to diagnosis, or symptom duration. A large pain study in Sweden found that individuals with EDS and hypermobility syndrome had longer pain duration than those suffering from whiplash, spinal pain, or fibromyalgia (Molander et al., 2020). Researchers have explored the association between disease duration and health outcomes in other chronic conditions with a high symptom burden, often with conflicting results. For example, Rollot et al. (2021) looked at age impact on disease duration in individuals with multiple sclerosis (MS). These researchers found age had a greater impact on mortality than disease duration in relapsing onset MS. Yet this same study also found mortality steadily increased from disease onset in primary progressive MS. Research on symptom trajectory in individuals with hEDS/HSD throughout the lifespan is needed to untangle the complicated associations among age, diagnosis delay, disease duration, and health outcomes. Such research necessitates sampling strategies that target older adults with hEDS/HSD.

The reported hEDS/HSD comorbidities and multisystemic manifestations identified in the included studies are consistent with previous research (Castori et al.,
2017; Tinkle et al., 2017) and have important implications for undiagnosed older adults who may present with multimorbidity. The heterogeneous and unpredictable nature of hEDS/HSD contributes to diagnosis and treatment delays because the multiple symptoms are shared with other conditions not uncommon in the aging population. A high number of comorbidities resulting from multiple healthcare interactions might lead to more incidental findings of other disorders or misdiagnosis of the heterogeneous EDS clinical manifestations due to body-wide, disordered connective tissue (Leganger et al., 2020). Researchers continue to debate whether diagnoses co-existing with hEDS/HSD are a cause or a result of hEDS/HSD, a distinct comorbid condition, or a possible misdiagnosis due to symptom overlap with other conditions. Whether these conditions are comorbidities or hEDS/HSD manifestations, more research is needed to identify symptom clusters and patterns to facilitate hEDS/HSD diagnosis in older adults.

Although the included studies failed to report an association between age and HRQOL in individuals with hEDS/HSD, this association has been reported in studies with other chronic conditions. Wysocka-Skurska et al. (2016) studied patients with arthritis and found that disease duration was associated with worse physical component SF-36 scores in both osteo- and rheumatoid arthritis and the mental component SF-36 scores in patients with osteoarthritis. Jiao et al. (2014) found that young and middle-aged individuals with fibromyalgia had significantly worse HRQOL than older individuals, with younger individuals having worse scores than those in middle age. Since De Wandele et al. (2014) noted autonomic symptom profile similarities between EDS-HT and fibromyalgia, the association between age and disease duration bears further exploration in people with hEDS/HSD.
Limitations

This study has limitations. The inclusion criteria used the terminology from the 2017 International Consortium diagnostic criteria labels and historic labels for hEDS/HSD. Given the variation in diagnostic terminology over the years, potentially relevant articles may have been excluded. Articles were also excluded if they used the terms for joint hypermobility and joint hypermobility syndrome interchangeably or aggregated all EDS types in the analyses, as the differences in phenotypic expression, morbidity, and mortality could significantly impact results. Inclusion criteria limited studies to those conducted within the past ten years to reflect the most current understanding of the topic, potentially missing relevant earlier studies. Also, consistent with guidelines for scoping reviews (Munn et al., 2018; Tricco et al., 2018), the authors did not conduct a formal risk of bias assessment of individual studies. Despite these limitations, this review provides valuable insight into the depth and breadth of existing knowledge about hEDS/HSD and aging.

Clinical and Research Implications

Unlike systematic reviews, Munn et al. (2018) urge caution in adopting practice changes based on scoping reviews without risk of bias appraisals. However, while no definitive conclusions can be drawn from this review about aging with hEDS/HSD, the described studies have clinical and research implications. These results, particularly the case study by Bergl et al. (2019), highlight clinicians’ difficulty evaluating older adults with a complicated history of multisystemic symptoms who may have undiagnosed hEDS/HSD. A timelier hEDS/HSD diagnosis will require more research into the clinical presentation of hEDS/HSD in individuals of all ages. Because hEDS/HSD symptoms are
multisystemic, this review reveals opportunities for future interdisciplinary research with implications for multiple clinical specialties. Finally, this review illuminates the need for studies with larger samples, more longitudinal studies, and more older participants to aid in earlier diagnosis, develop better prognostic models, and facilitate coordinated multidisciplinary treatment to maximize health outcomes in older adults with hEDS/HSD.

**Conclusion**

This review did not find studies describing how hEDS/HSD presents or progresses in older adults; however, the studies corroborated earlier research about the general symptom trajectory and impact in younger and middle-aged adults. Multiple comorbidities can delay clinicians’ recognition of a unifying connective tissue etiology, which can be particularly problematic in older adults. Symptoms of hEDS/HSD present and progress unpredictably, further contributing to diagnosis delays and poor HRQOL. This review highlights the need for more research into the clinical presentation, progression, and impact of aging in hEDS/HSD.
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Chapter Four

Hypermobile Ehlers-Danlos Syndrome/Hypermobility Spectrum Disorders in Older Women: A Feasibility Study


**Authorship Statement**

Linda K. Anderson performed the topic selection and development, survey design, participant recruitment, data collection, results synthesis, and drafted the initial manuscript. Kari R. Lane assisted in survey design and testing, results synthesis and critically reviewed the manuscript for important intellectual content. Both authors approved the final manuscript for publication.
Abstract

**Introduction.** Hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders cause joint instability, chronic pain, fatigue, and progressive multisystemic dysfunction, increasing symptom burden and decreasing quality of life. Researchers know little about how these disorders progress in women as they age. **Objective.** This research aimed to determine the feasibility of an internet-based study to understand the clinical characteristics, symptom burden, and health-related quality of life in older women with symptomatic hypermobility disorders. **Methods.** This cross-sectional, internet-based survey studied recruitment methods, suitability, and usability of survey instruments and obtained baseline data on women aged 50 and older with hEDS/HSD. Researchers recruited participants from a Facebook group for older adults with Ehlers-Danlos syndrome. Outcome measures included health history, the Multidimensional Health Assessment Questionnaire, and the RAND Short Form 36 health survey. **Results.** Researchers recruited 32 participants from a single Facebook group within two weeks. Nearly all participants were satisfied with the survey length, clarity, and navigation, with 10 participants providing free-text recommendations for survey improvement. The survey suggests a high symptom burden and poor quality of life in older women with hEDS/HSD. **Conclusion.** The results support the feasibility and importance of a future internet-based comprehensive study about hEDS/HSD in older women.

*Keywords:* Ehlers-Danlos syndrome, hypermobility spectrum disorders, joint instability, feasibility study, aging, older women, quality of life
Hypermobile Ehlers-Danlos Syndrome/Hypermobility Spectrum Disorders in Older Women: A Feasibility Study

Hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders (hEDS/HSD) represent a spectrum of heterogeneous inherited connective tissue disorders characterized by joint instability, tissue fragility, chronic pain, and progressive multisystem dysfunction (Castori et al., 2017; Tinkle et al., 2017). Symptoms of hEDS/HSD progress in severity over time, ultimately leading to functional disability and poor health-related quality of life (HRQOL; Berglund et al., 2015; Castori et al., 2011). Unpredictable, non-specific symptoms make hEDS/HSD challenging to diagnose, and diagnosis delays are common (Castori, 2012; Hamonet et al., 2017).

It is unclear how hEDS/HSD symptoms progress as women age. Poor understanding of the hEDS/HSD clinical presentation in older women can lead to diagnosis delays, ineffective treatments, surgical complications, and decreased HRQOL (Kulas Søborg et al., 2017; Tinkle et al., 2017). This knowledge gap calls for research on hEDS/HSD in older women to better understand hEDS/HSD presentation and clinical progression. Due to the low number and wide geographical distribution of potential participants, such research requires innovative methods, including internet-based recruitment, enrollment, and data collection (Gagne et al., 2014). The complexity of research in this population called for a feasibility study to evaluate and refine the proposed online research methods, including study announcements, recruitment rates, and the suitability of the online survey.

This research aimed to determine the feasibility of a future online study, including recruitment methods, suitability, and usability of data collection instruments and
procedures, to generate a comprehensive picture of hEDS/HSD in women aged 50 and older. Additionally, this research obtained baseline data on the demographics, clinical characteristics, and health-related quality of life in older women with hEDS/HSD.

**Methods**

**Study Design**

This online, cross-sectional, quantitative feasibility study used custom and validated instruments. Feasibility studies help determine whether or not researchers should undertake a particular study and assess recruitment strategies and outcomes (Danesh et al., 2021). The Institutional Review Board approved this study, and participants indicated their informed consent before the survey began.

**Setting and Sample**

The researchers recruited participants from a Facebook group of over 400 older adults diagnosed with some form of Ehlers-Danlos syndrome (EDS) between May 20 and June 2, 2022, with Facebook group administrator approval. Survey eligibility for this convenience sample included: (a) female, (b) age 50 years or older, (c) able to read and understand English, (d) self-reported diagnosis of hEDS/HSD (or one of its analogous diagnostic terms) by a healthcare provider, and (e) access to a computer and the internet for survey completion. No participant was excluded based on geographic location, race/ethnicity, education level, or other demographic variables beyond age and gender.

**Study Size**

Because this was a small feasibility study, the researchers performed no power calculation. The target sample size of 20-40 participants was considered adequate to
assess recruitment, estimate survey completion rates, and provide sufficient feedback for questionnaire and procedure refinement (Billingham et al., 2013).

Outcomes and Measures

Primary Outcomes

Feasibility. The primary outcome was study feasibility. Researchers conduct feasibility studies to estimate design parameters and determine if a more extensive study is practical and achievable (Danesh et al., 2021; Eldridge et al., 2016; Lancaster & Thabane, 2019). Feasibility studies are distinguished from pilot studies that focus on interventions and outcomes. Feasibility studies focus on the study’s process, including recruitment and sample characteristics, data collection instruments and outcome measures, study acceptability to participants, and resources needed to conduct the study (Orsmond & Cohn, 2015).

To measure feasibility, the researchers created a custom instrument with three items measured on a 5-point Likert scale from 0 = “Completely agree” to 5 = “Completely disagree” to measure survey length, clarity, and navigation. Lower scores indicated better usability. The minutes required to complete the survey were measured as a continuous variable. The survey included two optional, free-text questions related to study feasibility and content:

1. “Do you have any suggestions or recommendations about how to make this survey more clear or easier to understand?”

2. “Do you have suggestions or recommendations about additional topics to include in a study about hEDS/HSD in older women?”

Secondary Outcomes
**Sociodemographic Information and Health History.** The researchers designed a custom instrument to measure sociodemographic data and health history, including age, country of birth and current residence, self-described race or ethnic group, years of education, marital status, work status, home or living situation, and current perceived physical ability. Health history included ages of symptom onset and diagnosis, clinical specialty of diagnosing provider, and additional diagnoses. These sociodemographic and health history variables were measured using a combination of numeric, Likert-scale, and checklist items.

**Clinical Characteristics.** The Multidimensional Health Assessment Questionnaire measured clinical characteristics (MDHAQ; Pincus et al., 1999, 2009). The MDHAQ, designed to measure disease progression and treatment impact on rheumatology patients, produces six scores, including (a) function (FN), (b) pain (PN), (c) fatigue (FT), (d) Patient Global Assessment (PATGL), (e) Rheumatoid Arthritis Disease Activity Index (RADAi), and (f) Review of Systems symptom checklist (ROS). These scales were used to calculate cumulative indices, including (a) Routine Assessment of Patient Index Data 3 (RAPID3) and (b) Fibromyalgia Assessment Screening Tool 4 (FAST4). Higher numbers on the MDHAQ scales and cumulative indices indicate worse disease status. Psychometric tests of the MDHAQ on rheumatology patients showed good test-retest reliability with Kappa scores 0.65-0.81 (Pincus et al., 1999) and good internal consistency with Cronbach’s alpha 0.871-0.906 (Leeb et al., 2009). Researchers in the U.K. used the MDHAQ to measure physiotherapy outcomes in individuals with hypermobility disorders (Palmer et al., 2016).
HRQOL. The RAND Short Form Health Survey measured HRQOL (SF-36; Ware & Sherbourne, 1992). The SF-36 measures health status in eight domain scales: (a) Physical Function (PF), (b) Role Limitations-Physical (RP), (c) Bodily Pain (BP), (d) General Health (GH), (e) Vitality (VT), (f) Social Functioning (SF), (g) Role Limitations-Emotional (RE), and (h) Mental Health (MH). These domain scales are used to derive two summary measures: (a) Physical Component Summary (PCS) and Mental Component Summary (MCS). Higher numbers on the SF-36 domain and summary scores indicate better health and HRQOL. The SF-36 has demonstrated good internal consistency, with Cronbach’s alpha 0.73-0.97 (Brazier et al., 1992) and acceptable test-retest reliability of 0.60-0.81 (Brazier et al., 1992). The SF-36 domain scales show good internal consistency, with Cronbach’s alpha 0.93 for the PCS and 0.88 for the MCS (Ware et al., 1994). The SF-36 domain scales show excellent test-retest reliability in the general female population of 0.92 for the PCS and 0.90 for the MCS (Ware et al., 1994). Researchers have used the SF-36 to measure health status and HRQOL in hEDS/HSD studies (Berglund et al., 2015; Bovet et al., 2016; Johannessen et al., 2016) and Schubart et al. (2019) used it to delineate symptom severity clusters in patients with EDS (Schubart; et al., 2019).

Procedure

The initial survey internet link and draft questionnaire were pre-tested with a small convenience sample of the school of nursing faculty and students. The purpose of pre-testing the survey was to determine the functionality of the study’s internet link, instructions, question-wording, and response-based question flow (Roopa & Rani, 2012). After successful pre-testing, the researchers posted an announcement on the Facebook
group containing study information and a survey link. This link led to an introductory screen containing study information, researchers’ contact information, and informed consent. Upon online acknowledgment of informed consent, participants were directed to the rest of the survey. If participants declined consent, they were directed to a site thanking them for their time, thereby terminating the survey. Participants received no compensation for this study.

Data Analysis

Study data were collected and managed using the Research Electronic Data Capture (REDCap) tools. REDCap is a secure, web-based application that supports data capture, analysis, and audit trails for research studies (Harris et al., 2009). All survey responses were exported from REDCap into SPSS Statistics for Windows, Version 27.0 for quantitative analyses. Data were manually checked for errors, missing responses, and outliers. As a feasibility study with a small sample, no inferential statistics, controlling for confounders, or subgroup analyses were performed. Descriptive statistics for numeric variables were reported using medians and interquartile ranges due to the skewed data distribution. Descriptive statistics for categorical variables were reported as frequencies and percentages.

Impact of COVID-19 on Study

This study was conducted approximately two years into the COVID-19 pandemic. As this was a cross-sectional online survey, any impact of pandemic illness or restrictions on participants or researchers was deemed negligible. This study required no modification to the survey, data analysis, or interpretation due to pandemic factors.
Results

Researchers posted the study announcement on a single Facebook group for older adults with EDS, which produced 11 submitted surveys. A follow-up announcement after one week yielded 21 additional surveys. Recruitment was closed after two weeks, with 32 participants. A total of 32 participants consented to the study, with two surveys abandoned with less than 5% of fields completed. Table 4.1 shows the sociodemographic profile of the participants. The median age was 62, with most participants residing in the United States. Most participants were married; disabled or retired; living with a spouse, partner, or children; and considered themselves independent or mostly independent. All participants were white.

Table 4.1

Sociodemographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>Median or Frequency</th>
<th>IQR or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current age (yr)</td>
<td>30</td>
<td>62.0</td>
<td>55.0-65.0</td>
</tr>
<tr>
<td>Education</td>
<td>29</td>
<td>18.0</td>
<td>15.0-20.0</td>
</tr>
<tr>
<td>Country of residence</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>23</td>
<td>76.7</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>3</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>3</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>1</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>20</td>
<td>69</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>5</td>
<td>17.2</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>2</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>2</td>
<td>6.9</td>
<td></td>
</tr>
<tr>
<td>Employment</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disabled</td>
<td>12</td>
<td>41.4</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>7</td>
<td>24.1</td>
<td></td>
</tr>
<tr>
<td>Employed full-time</td>
<td>6</td>
<td>20.7</td>
<td></td>
</tr>
</tbody>
</table>
Self-employed 3 10.3
Employed part-time 1 3.4

Housing 29
Live with spouse or partner or children 21 72.4
Live alone 5 17.2
Live with parent(s) or sibling(s) 2 6.9
Share housing with others (not related) 1 3.4

Current ability 27
Independent or mostly independent 18 66.7
Mostly housebound 8 29.6
Bedbound 1 3.7

Note. IQR, interquartile range (Q1-Q3); UK, United Kingdom; US, United States

Table 4.2 summarizes the survey’s feasibility. Most participants were satisfied with the survey length, clarity, and navigation. Nearly one-third of participants provided optional free-text recommendations to improve the survey instrument or process. One participant stated, “…I thought the survey was very clear and concise enough that anyone should be able to complete it.” A few participants commented on the redundancy or wording of the survey questions: “Felt question redundancy,” and “I felt that depression was being belittled by calling it ‘feeling blue’….”

Table 4.2

Suitability and Usability of Data Collection Procedures and Instruments

<table>
<thead>
<tr>
<th>Survey Item</th>
<th>n</th>
<th>Completely agree</th>
<th>Somewhat agree</th>
<th>Neither agree nor disagree</th>
<th>Somewhat disagree</th>
<th>Completely disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>This survey was an appropriate length (took an appropriate amount of time to complete)</td>
<td>25</td>
<td>20 (80%)</td>
<td>3 (12%)</td>
<td>2 (8%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Question</td>
<td>N</td>
<td>1 (4%)</td>
<td>2 (8%)</td>
<td>3 (12%)</td>
<td>21 (84%)</td>
<td>Other</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>---</td>
<td>--------</td>
<td>--------</td>
<td>---------</td>
<td>----------</td>
<td>-------</td>
</tr>
<tr>
<td>This survey was clear and easy to understand.</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>This survey was easy to navigate and complete.</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How much time (in minutes) did it take for you to complete this survey?</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What suggestions or recommendations do you have about making the survey clearer or easier to navigate?</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free text questions (optional)</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Illustrative Quotes/Comments</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have suggestions or recommendations about additional topics to include in a study about hEDS/HSD in older women?</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- “Felt question redundancy.”
- “Clear and easy, just might include questions of healthcare and understanding of healthcare professionals…”
- “Avoid double negatives (ie asking a negative framed question)”
- “I felt that depression was being belittled by calling it ‘feeling blue’ …it is so much more than feeling blue…”
- “…I thought the survey was very clear and concise enough that anyone should be able to complete it.”
- “The one issue was with the age of last period…it let me go forward but I had to click several times.”
- “I thought it was very clear.”
- “It was a little difficult to determine between physical and mental. Maybe if purely physical answers were labeled as such.”
- “I found it clear and easy to complete. Thank you.”

- “…how we are doing as we age…”
- “Any surgical interventions or external bracing needed for joints.”
- “be sure to investigate all possible extra conditions…specifically about autoimmune conditions to investigate the correlation.”
- “…expectation for aging…”
- “If HRT helps? Increases energy? Decrease pain or stiffness or subluxations”
- “Perhaps ask at what age the hypermobility began to interfere with their life.”
“Yes questions about support systems. All my siblings died prior to age 60, many of my friends have died and I find it's very hard to replace/rebuild a support system when I am not very active anymore. It’s a major concern for me.”

Note. hEDS, hypermobile Ehlers-Danlos syndrome; HRT, hormone replacement therapy; HSD, hypermobility spectrum disorder

Table 4.3 shows health history. The median age of hEDS/HSD symptom onset was six years, with a median time of 50 years between symptom onset and diagnosis. Most participants were diagnosed with hypermobility disorder by a geneticist. The median age of onset of the first menstrual period was 12, and the median number of pregnancies was three. Most participants reported hEDS/HSD symptoms worsened with periods of hormonal fluctuation, including puberty, pregnancy, and menopause. Participants reported multiple comorbidities, with 50% or more reporting diagnoses of osteoarthritis, gastrointestinal reflux disease, temporomandibular dysfunction, anxiety, irritable bowel syndrome, postural orthostatic tachycardia syndrome, fibromyalgia, and depression. Figure 4.1 displays additional diagnoses frequency reported by participants. Table 4.4 shows health outcomes measured by the MDHAQ and the SF-36. MDHAQ and SF-36 scores displayed a high symptom burden and poor HRQOL. Overall, participants reported poor physical function, high pain, and high fatigue. Scores were worse in the physical domains than in the mental/emotional domains.
Table 4.3

*Health History*

<table>
<thead>
<tr>
<th>Variable</th>
<th>$n$</th>
<th>Median or Frequency</th>
<th>IQR or %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass index</td>
<td>29</td>
<td>30.7</td>
<td>26.8-38.2</td>
</tr>
<tr>
<td>Age at symptom onset</td>
<td>29</td>
<td>6.0</td>
<td>3.0-10.5</td>
</tr>
<tr>
<td>Age at diagnosis (yr)</td>
<td>29</td>
<td>55.0</td>
<td>45.0-58.0</td>
</tr>
<tr>
<td>Time to diagnosis (yr)</td>
<td>29</td>
<td>50.0</td>
<td>29.0-53.5</td>
</tr>
<tr>
<td>Diagnosing provider</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geneticist</td>
<td>14</td>
<td>46.7</td>
<td></td>
</tr>
<tr>
<td>Rheumatologist</td>
<td>8</td>
<td>26.7</td>
<td></td>
</tr>
<tr>
<td>Primary care provider</td>
<td>3</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Orthopedist</td>
<td>1</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Physical therapist/physiotherapist</td>
<td>1</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Chiropractor</td>
<td>1</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Age first menstrual period</td>
<td>26</td>
<td>12.0</td>
<td>11.0-14.0</td>
</tr>
<tr>
<td>Puberty impact on hEDS/HSD symptoms ($n = 26$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms began</td>
<td>3</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td>Symptoms got worse</td>
<td>8</td>
<td>30.8</td>
<td></td>
</tr>
<tr>
<td>Symptoms got better</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No change in symptoms</td>
<td>5</td>
<td>19.2</td>
<td></td>
</tr>
<tr>
<td>Don’t remember</td>
<td>10</td>
<td>38.5</td>
<td></td>
</tr>
<tr>
<td>Total number of pregnancies</td>
<td>3</td>
<td>2.0-5.0</td>
<td></td>
</tr>
<tr>
<td>Live births</td>
<td>2</td>
<td>1.0-3.0</td>
<td></td>
</tr>
<tr>
<td>Pregnancy impact on hEDS/HSD symptoms ($n = 22$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms got worse</td>
<td>10</td>
<td>45.5</td>
<td></td>
</tr>
<tr>
<td>Symptoms got better</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No change in symptoms</td>
<td>4</td>
<td>13.8</td>
<td></td>
</tr>
<tr>
<td>More than 1 pregnancy, symptoms differed between pregnancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Don’t remember</td>
<td>4</td>
<td>18.2</td>
<td></td>
</tr>
<tr>
<td>Age last menstrual period</td>
<td>22</td>
<td>49.0</td>
<td>41.5-52.25</td>
</tr>
</tbody>
</table>
Menopause impact on hEDS/HSD symptoms ($n = 23$)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms got worse</td>
<td>14</td>
<td>60.9</td>
</tr>
<tr>
<td>Symptoms got better</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No change in symptoms</td>
<td>4</td>
<td>17.4</td>
</tr>
<tr>
<td>Don’t remember</td>
<td>5</td>
<td>21.7</td>
</tr>
</tbody>
</table>

*Note.* BP, bodily pain; FN, function; FT, fatigue; GH, general health; IQR, interquartile range (Q1-Q3); MCS, mental component summary; MDHAQ, Multidisciplinary Health Assessment Questionnaire; MH, mental health; PATGL, patient global assessment; PCS, physical component summary; PF, physical function; PN, pain; RADAI, rheumatoid arthritis disease activity index; RAPID3, routine assessment of patient index data; RE, role limitations - emotional; ROS, review of systems; RP, role limitations - physical; SF-36, Short Form 36; SF, social function; VT, vitality

**Figure 4.1**

*Additional Diagnoses Reported by Participants*
Note. ASD, autism spectrum disorder; GERD, gastrointestinal reflux disease; IBS, irritable bowel syndrome; MVP, mitral valve prolapse, POTS, postural orthostatic tachycardia syndrome, TMJ, temporomandibular joint dysfunction

**Table 4.4**

*Health Outcomes*

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Median (IQR)</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MDHAQ (ranges vary)</strong></td>
<td></td>
<td><strong>Lower numbers = better outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>FN (range 0–10)</td>
<td>25</td>
<td>2.0 (0.8-4.8)</td>
<td>2.8 (2.1)</td>
</tr>
<tr>
<td>PN (range 0-10)</td>
<td>26</td>
<td>7.0 (4.5-8.1)</td>
<td>6.5 (2.2)</td>
</tr>
<tr>
<td>PATGL (range 0–10)</td>
<td>25</td>
<td>5.0 (3.8-8.0)</td>
<td>5.5 (2.6)</td>
</tr>
<tr>
<td>RADAI (range 0-48)</td>
<td>20</td>
<td>20.5 (10.3-25.8)</td>
<td>20.3 (10.98)</td>
</tr>
<tr>
<td>RAPID3 (range 0–30)</td>
<td>24</td>
<td>15.5 (9.6-19.7)</td>
<td>15.2 (5.9)</td>
</tr>
<tr>
<td>ROS (range 0–60)</td>
<td>26</td>
<td>23.5 (19.8-29.3)</td>
<td>24.2 (9.4)</td>
</tr>
<tr>
<td>FT (range 0–10)</td>
<td>26</td>
<td>7.0 (5.4-9.3)</td>
<td>7.3 (2.2)</td>
</tr>
<tr>
<td><strong>SF-36 (all ranges 0-100)</strong></td>
<td></td>
<td><strong>Higher numbers = better outcomes</strong></td>
<td></td>
</tr>
<tr>
<td>PF</td>
<td>24</td>
<td>35.0 (11.3-68.8)</td>
<td>38.5 (28.0)</td>
</tr>
<tr>
<td>RP</td>
<td>25</td>
<td>0 (0-37.5)</td>
<td>23.0 (38.9)</td>
</tr>
<tr>
<td>RE</td>
<td>25</td>
<td>33.3 (0-100)</td>
<td>44.0 (45.9)</td>
</tr>
<tr>
<td>VT</td>
<td>23</td>
<td>20.0 (0-30.0)</td>
<td>20.0 (17.1)</td>
</tr>
<tr>
<td>MH</td>
<td>24</td>
<td>64.0 (48.0-72.0)</td>
<td>61.0 (15.2)</td>
</tr>
<tr>
<td>SF</td>
<td>24</td>
<td>37.5 (12.5-50.0)</td>
<td>39.6 (28.0)</td>
</tr>
<tr>
<td>BP</td>
<td>25</td>
<td>32.5 (22.5-50.0)</td>
<td>35.4 (19.7)</td>
</tr>
<tr>
<td>GH</td>
<td>25</td>
<td>25.0 (10.0-35.0)</td>
<td>23.4 (15.6)</td>
</tr>
<tr>
<td>PCS</td>
<td>21</td>
<td>25.2 (19.3-34.8)</td>
<td>26.5 (10.1)</td>
</tr>
<tr>
<td>MCS</td>
<td>21</td>
<td>41.3 (33.5-48.3)</td>
<td>40.4 (9.0)</td>
</tr>
</tbody>
</table>

Note. BP, bodily pain; FN, function; FT, fatigue; GH, general health; IQR, interquartile range (Q1-Q3); MCS, mental component summary; MDHAQ, Multidisciplinary Health Assessment Questionnaire; MH, mental health; PATGL, patient global assessment; PCS, physical component summary; PF,
This study suggests that an internet-based study using online recruitment, screening, and administration can yield a greater understanding of hEDS/HSD in older women. The survey was deemed suitable and usable by participants, who provided suggestions for instrument improvement. This feasibility study revealed the need to include additional specialties in health provider fields, including a pulmonologist, oncologist, pain management, and child’s provider. Participants recommended adding a child’s provider as some adults were diagnosed after a pediatrician or pediatric geneticist diagnosed their child. This study asked for the participant’s current diagnosis, but participants recommended a question about the original diagnosis, as their diagnoses often changed based on provider specialty or currently accepted terminology. Participants suggested additional topics for the survey, including social support systems and the effectiveness of therapeutic interventions such as bracing, surgeries, and hormone replacement therapy.

This study yielded valuable information for researchers designing a future study on older women with hEDS/HSD. Despite careful attention to question content and wording in the custom portions of the survey, participants perceived redundancy and repetition due to using two standardized questionnaires with similar items. Researchers should inform the participants that they may encounter similar questions due to using
copyrighted questionnaires and emphasize the importance of answering all questions for accurate statistical analysis.

This study generated baseline data about the clinical characteristics and HRQOL in older women with hEDS/HSD. Long diagnosis delays, multiple comorbidities, high symptom burden, and poor HRQOL have been identified in hEDS/HSD studies in younger patients (Berglund et al., 2015; Castori, 2012; Tinkle et al., 2017). In the present study, each MDHAQ scale and cumulative index scores were comparable to other studies with middle-aged rheumatology patients (El Haddad et al., 2017; Schmukler et al., 2019) and were worse than a similar feasibility study in patients with hypermobility syndrome whose sample mean age was 34 (Palmer et al., 2016). Also, this study’s SF-36 domain and summary scores were comparable to a recent study on patients with hEDS with a sample mean age of 45 (Hakimi et al., 2020). These results suggest an overall worsening of symptoms and a greater impact on HRQOL, particularly in physical domains. However, this study points to a need for more research into the trajectory of specific symptoms, the influence of lifestyle factors, and the impact of healthcare interactions on functional disability and HRQOL,

This study has limitations. The risk of sampling bias is high, as the participants were recruited from a single Facebook group specifically for older adults with hEDS/HSD. Internet anonymity, participant self-selection, and recall bias may impact study validity. Furthermore, since this study was entirely online, researchers could not confirm hEDS/HSD diagnosis or health history. Analysis was limited to descriptive statistics due to the small sample size and resulting skewed distributions. We also note limited racial and ethnic diversity in this sample, as all participants identified as
Caucasian, were from developed countries, and were highly educated. A definitive study will employ a larger sample size, using multivariate statistics, and recruit from multiple sources to mitigate some of these risks to internal and external validity.

**Conclusion**

These results suggest that a definitive, internet-based study recruiting from EDS social media groups is feasible. The long diagnosis delays, multiple comorbidities, and poor health outcomes indicate the need for a better understanding of the clinical presentation and disease progression of hEDS/HSD in older women. Better knowledge of hEDS/HSD presentation and symptom progression as women age may lead to faster diagnosis and improved treatments, thereby improving clinical outcomes and reducing functional disability.
References


Pincus, T., Mandelin, A. M. II, & Swearingen, C. J. (2009). Flowsheets that include

https://doi.org/10.1002/1529-0131(199910)42:10<2220::AID-ANR26>3.0.CO;2-5


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https://doi.org/10.1002/ajmg.c.31538
Ware, J. E., Jr., Kosinski, M., & Keller, S. D. (1994). *SF-36 physical and mental health summary scales: A user's manual*. Health Assessment Lab, New England Medical Center

Chapter Five

Methods

Introduction

This chapter describes the research approach and methods used to assess the demographic factors, clinical characteristics, and HRQOL in midlife and older women with hEDS/HSD.

In 2022, a preliminary study determined the feasibility of an online survey to understand the clinical characteristics, symptom burden, and health-related quality of life in older women with hEDS/HSD (Anderson & Lane, 2023). Researchers recruited 32 participants from a Facebook group for adults aged 50 and over diagnosed with EDS. The results suggested that recruiting from EDS social media groups was feasible. Participants also suggested additional survey content, including more comorbid diagnoses, response to hormone replacement therapy, and information on surgical interventions and mobility aids including braces. These recommendations were included in the present survey. The baseline measurements showed long diagnosis delays, multiple comorbidities, and poor health outcomes indicate the need to study the clinical presentation and disease progression of hEDS/HSD in midlife and older women.

Methodology

This internet-based, cross-sectional survey study aimed to comprehensively understand hEDS/HSD in midlife and older women and identify the factors that influence HRQOL in this population. The survey was comprised of custom and validated instruments and four free-text open-ended questions to provide further detail and context.
Theoretical Framework

The International Classification of Functioning, Disability and Health (ICF), a biopsychosocial model from the World Health Organization that blends medical and social models of disability, provided the theoretical framework for this study (World Health Organization [WHO], 2001). This framework is in two parts: Part One deals with functioning and disability, classified into two domains: (a) the body, including body functions and structures, and (b) activities and participation. Part Two of the ICF deals with contextual factors that influence functioning, including (a) environmental and (b) personal characteristics. The ICF establishes a common patient-centered and multidisciplinary language and systematic coding scheme for health states that facilitates the comparison of health-related data across locations, disciplines, and time (WHO, 2001). The ICF is patient-centered, globally adopted, and is an appropriate framework for understanding complex disabling conditions, making it useful in understanding the impact of hEDS/HSD in midlife and older women (Jacobs et al., 2018; Johannessen et al., 2018; Scheper et al., 2016).

Sample

Study Site and Recruitment

This study recruited participants from EDS Facebook and social media sites with site administrator or moderator approval. All data from the online surveys were collected between May 31 and June 30, 2023.

Sample Size

The survey sample size was based on published sample size recommendations for the Short-Form 36 PCS and MCS summary score comparisons between a group mean
and a population norm (Prieto et al., 1996). For a moderate effect size of 0.5, defined as
the standard mean difference (SMD) between the sample and a population norm, the
recommended sample size was 64, assuming a two-tailed t-test, 80% power, and \( p < .05 \).
This study increased that total by approximately 15% to account for missing data, making
the target sample size for this study 75.

**Inclusion and Exclusion Criteria**

Survey eligibility criteria included (a) female, (b) age 40 years or older at the time
of survey completion, (c) able to read and understand English, (d) diagnosis of
hEDS/HSD by a licensed healthcare provider, and (e) access to a computer with internet
capability. This study anticipated participants would include U.S. and non-U.S.
participants and excluded no participants based on geographic location. The minimum
age of 40 was chosen because skin and tissue elasticity decreases abruptly in women’s
40s, possibly due to the hormonal fluctuations of perimenopause (Luebberding et al.,
2013). Furthermore, a minimum age of 40 would allow researchers to compare outcomes
between pre- and postmenopausal women. Race/ethnicity, education level, and other
demographic variables beyond age and gender were unknown at study enrollment but
were collected during the survey.

**Method**

**Procedure**

Study announcements on EDS social media sites linked interested respondents to
a website for screening. A webpage link connected respondents who met the eligibility
criteria to the study description and consent form. After indicating online consent, a link
directed participants to the survey. If a respondent failed to meet eligibility criteria or
elected not to participate, the website directed them to an online page thanking them for their time.

**Data Collection**

Variables were linked into broad ICF categories representing functioning, disability, and health. A custom questionnaire measured sociodemographic and clinical characteristics, including health history. The Multidimensional Health Assessment Questionnaire (MDHAQ) measured symptom characteristics. The Craig Hospital Inventory of Environmental Factors Short Form (CHIEF-SF) measured environmental factors. The Short Form Health Survey (SF-36) measured HRQOL. The variables and study instruments are described below. Table 5.1 provides further variable details, including instrument scoring, psychometric measures, and associated ICF categories.

**Table 5.1**

*Variables Measuring Characteristics of Midlife and Older Women with hEDS/HSD*

<table>
<thead>
<tr>
<th>Variable Category</th>
<th>Measure</th>
<th>Scoring</th>
<th>ICF a</th>
<th>Psychometrics</th>
</tr>
</thead>
</table>
| Socio-demographic characteristics | • Current age  
• Years of education | Current age (continuous; stratify in 10-year age groups starting age 40)  
Years education (continuous) | Contextual Factors  
(b) Personal Factors: (not numerically coded in ICF) | NA – Custom instrument |
| | • Sex assigned at birth  
• Country: birth and current  
• Race/ethnic group  
• Marital status  
• Work status  
• Home/living situation  
• Current physical ability | | | |

Dichotomous (yes/no) brief free-text and Likert-scale responses
<table>
<thead>
<tr>
<th>Variable Category</th>
<th>Measure</th>
<th>Scoring</th>
<th>ICF *</th>
<th>Psychometrics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td><strong>Health History</strong></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• Age symptom onset</td>
<td>Continuous</td>
<td></td>
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<tr>
<td></td>
<td>• Age diagnosis</td>
<td>Time to diagnosis</td>
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<tr>
<td></td>
<td>• Time to diagnosis (age diagnosis – age symptom onset)</td>
<td>(age diagnosis – age symptom onset)</td>
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<tr>
<td></td>
<td>• Symptom duration (current age – age symptom onset; continuous)</td>
<td>Symptom duration (current age – age symptom onset)</td>
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<tr>
<td></td>
<td><strong>Symptom Characteristics:</strong></td>
<td>Higher scores = worse status</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• MDHAQ Function (FN)</td>
<td>FN: 3-point Likert scale; score converted per template; range 0-10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• MDHAQ Pain (PN)</td>
<td>PN, FT, PATGL: 21-point visual analog scale in 0.5-unit increments; range 0-10</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• MDHAW Fatigue (FT)</td>
<td>RADAI: number/severity of painful joints; 0 = “None” to 3 = “Severe”; range 0-48</td>
<td></td>
<td></td>
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<td></td>
<td>• MDHAQ Patient Global (PATGL)</td>
<td>ROS: 60-item symptom checklist: dichotomous; symptom present (1 point); range 0-60</td>
<td></td>
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<tr>
<td></td>
<td>• MDHAQ Rheumatoid Arthritis Disease Activity Index (RADAI)</td>
<td>RAPID3: Sum of RADAI, PN, FT, ROS; converted per template; range 0-4</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• MDHAQ Review of Systems (ROS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• MDHAQ Routine Assessment of Patient Index Data 3 (RAPID3; range 0-30)</td>
<td></td>
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<tr>
<td></td>
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<tr>
<td></td>
<td><strong>Functioning and Disability</strong></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>(a) Body Functions and Structures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Pain (b280-b289)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Functions of joints and bones (b710-b729)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Movement functions (b750-b789)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td><strong>Comorbid diagnoses</strong></td>
<td>Dichotomous (no = 0; yes = 1)</td>
<td></td>
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<tr>
<td></td>
<td></td>
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<tr>
<td></td>
<td><strong>Surgical procedures</strong></td>
<td>Dichotomous (no = 0; yes = 1)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Variable Category</td>
<td>Measure</td>
<td>Scoring</td>
<td>ICF *</td>
<td>Psychometrics</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------</td>
<td>---------</td>
<td>-------</td>
<td>---------------</td>
</tr>
</tbody>
</table>
| **Women’s Health:** | • Age first menstrual period  
• Age last menstrual period  
• More than 1 year since LMP  
• Impact on symptoms  
• Puberty  
• Pregnancy  
• Menopause  
• Hormonal contraceptives  
• Hormone replacement therapy  
• Number of pregnancies  
• Number of live births  
• Pregnancy or childbirth complications  
• Obstetrical and gynecological symptoms | Ages of puberty, menopause; number pregnancies (continuous)  
Impact on symptoms (Likert-scale)  
Pregnancy or childbirth complications, obstetric and gynecological symptoms (categorical) | Contextual Factors  
(b) Personal Factors:  
(not numerically coded in ICF) | NA - Custom instrument |
| **Environment characteristics** | **Craig Hospital Inventory of Environmental Factors Short Form**  
(CHIEF-SF) 12-item instrument to measure frequency and magnitude of environmental barriers in the past 12 months  
• Policy Subscale  
• Physical/Structural subscale  
• Work/School subscale  
• Attitudes/Support subscale  
• Services/Assistance subscale | Higher scores = more barriers  
Ordinal; results reported as average frequency score (0=never to 4=daily) average magnitude score (1=little problem to 2-big problem), and average frequency x magnitude product score; each item score range 0-8 across all non-missing scales; higher scores = more barriers | Contextual Factors:  
Contextual/environmental factors  
• Policy Subscale - Services, systems, policies (e510-e599)  
• Physical/Structural subscale – Natural environment and human-made changes to environment (e210-e299)  
• Work/School subscale: Produces and technology (e110-e199) and Services, systems, policies (e510-e599)  
• Attitudes/Support subscale - Support and relationships (e310-e399) and Attitudes (e410-e499)  
• Services/Assistance subscale - Services, systems, policies (e510-e599) | CHIEF-SF Subscales  
• Cronbach’s alpha 0.76 (Services/Assistance subscale) to 0.81 (Work/School subscale)  
Test-retest reliability  
• ICCs 0.77 (Policies subscale) to 0.891 (Attitudes/Support subscale)  
(Whiteneck et al., 2004) |
| **Assistive Devices** | Likert-scale  
(0=no; 1=use part) | Environmental Factors: | NA – Custom instrument |
<table>
<thead>
<tr>
<th>Variable Category</th>
<th>Measure</th>
<th>Scoring</th>
<th>ICF *</th>
<th>Psychometrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical and Mental HRQOL</td>
<td>RAND Short-Form 36 36-item instrument to measure health status during the past 4 weeks</td>
<td>Higher scores = better health status</td>
<td>(e) Products and technology (e110-e199)</td>
<td><strong>SF-36 Overall</strong></td>
</tr>
<tr>
<td></td>
<td>Domain Scales:</td>
<td></td>
<td></td>
<td>• Internal consistency Cronbach’s alpha 0.73-0.97 (Brazier et al., 1992)</td>
</tr>
<tr>
<td></td>
<td>• Physical Function (PF)</td>
<td></td>
<td></td>
<td>• Test-retest reliability 0.60-0.81 (Brazier et al., 1992)</td>
</tr>
<tr>
<td></td>
<td>• Role Limitations – Physical (RP)</td>
<td></td>
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<td></td>
<td>• Role Limitations – Emotional (RE)</td>
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<tr>
<td></td>
<td>• Vitality (VT)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Mental Health (MH)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Social Function (SF)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>• Bodily Pain (BP)</td>
<td></td>
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<tr>
<td></td>
<td>• General Health (GH)</td>
<td></td>
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<tr>
<td>Summary Scales</td>
<td>Summary scales: Computed by multiplying each SF-36 domain z-score by its respective factor score coefficient (physical factor score for PCS and mental factor score for MCS) and summing the eight products: ranges 0-100</td>
<td></td>
<td></td>
<td><strong>SF-36 Summary Scales</strong></td>
</tr>
<tr>
<td>Physical Component Summary (PCS)</td>
<td></td>
<td></td>
<td></td>
<td>• Internal consistency US general population 0.93 PCS and 0.88 MCS (Ware et al., 1994)</td>
</tr>
<tr>
<td>Mental Component Summary (MCS)</td>
<td></td>
<td></td>
<td></td>
<td>• Test-retest reliability general population females 0.92 PCS and 0.90 MCS (Ware et al., 1994)</td>
</tr>
</tbody>
</table>

*Note.* In the ICF, ACTIVITIES refers to the execution of a task or action by an individual. PARTICIPATION refers to involvement in a life situation. In this model, the ACTIVITIES and PARTICIPATION domains are combined into a single component, which is an option in the ICF (WHO, 2001). Some instrument composite scores may have items in one than one ICF category.
**Sociodemographic and Clinical Characteristics.** A custom instrument measured sociodemographic and clinical variables. Sociodemographic variables included age, biological sex at birth, country of birth and current residence, race/ethnic group, years of education, marital status, work status, current living situation, and physical activity level. Health history variables included height/weight/BMI, ages at symptom onset and diagnosis, original diagnosis, current diagnosis, diagnosing provider, comorbid diagnoses, gynecological and pregnancy history, and menopausal status.

**MDHAQ.** The MDHAQ is a multi-item, multi-format self-report questionnaire designed for rheumatology clinical assessment and research (Pincus et al., 1999). The MDHAQ provides scale measures for function, pain, fatigue, review of systems (ROS), self-report of global health assessment, and index measures, including the Routine Assessment of Patient Index Data 3 (RAPID3) and the Rheumatoid Arthritis Disease Activity Index (RADAI). The MDHAQ was designed for patients with rheumatoid arthritis but has been used in hEDS/HSD studies for its utility in musculoskeletal and multisystemic measures (Anderson & Lane, 2023; Palmer et al., 2016). The MDHAQ was free to use for academic research with attribution (Pincus et al., 1999). The copyright owner gave written permission for its use in this and a previous study.

**SF-36.** The SF-36 is a 36-item self-report questionnaire measuring health status during the previous four weeks using Likert- and dichotomous responses (Ware & Sherbourne, 1992; Ware et al., 1993, 1994). The SF-36 organizes items into eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The SF-36 also provides two summary measures, the Physical Component Summary (PCS) and the Mental Component
Summary (MCS) scales. Most people can complete the SF-36 in approximately 5 minutes (Brazier et al., 1992). Age- and sex-stratified US norms for the domain and summary scores have been published (Ware et al., 1993, 1994). Researchers have used the SF-36 to measure health status and HRQOL in many hEDS/HSD studies (Anderson & Lane, 2023; Berglund et al., 2015; Bovet et al., 2016; Johannessen et al., 2016) and have used it to delineate symptom severity clusters in patients with EDS (Schubart et al., 2019). Researchers have mapped the physical and mental health summary scores to ICF codes (Cieza et al., 2002, 2005; Lee & Song, 2018). The SF-36 version 1 was free to use with attribution to RAND and acknowledgment of its development as part of the Medical Outcomes Study (RAND, n.d.).

**CHIEF-SF.** The CHIEF-SF is a 12-item self-report questionnaire designed to measure the frequency and magnitude of environmental barriers encountered in the previous 12 months (Craig Hospital, 2001). Five subscale scores include policies, physical/structural, work/school, attitudes/support, and services) are derived from the item scores. The CHIEF-SF and the CHIEF full forms were developed to reflect the environmental factors conceptualized within the ICF framework (Whiteneck et al., 2004). The CHIEF-SF has been used to assess perceived environmental barriers, primarily in persons with stroke, traumatic brain injury, and spinal cord injuries. It has yet to be used in published hEDS/HSD studies. The CHIEF-SF was free to use, and the copyright holder permitted its use in this study (D. Mellick, personal communication, July 11, 2022).
Statistical Analysis

Data were collected and managed using Research Electronic Data Capture (REDCap), a secure, web-based application that supports data capture, analysis, and audit trails for research studies (Harris et al., 2009). Data were uploaded into SPSS version 29.0 for analysis. Participant responses were included in the analysis if complete enough to calculate primary and secondary outcomes of interest, and no data were imputed. All tests were 2-tailed, as there was no hypothesized direction of a relationship. The significance level was $p < .05$.

**Aim 1**

The personal, clinical, environmental, and HRQOL characteristics were analyzed using descriptive statistics (means, medians, standard deviations, frequencies, proportions). Shapiro-Wilk tests and visual examination of histograms and Q-Q plots revealed that many variables were not normally distributed, so most outcomes were analyzed using non-parametric tests. Age was analyzed as a continuous variable and was further stratified into 10-year age groups beginning at age 40. A study on JHS symptom mobility progression used a 10-year subgroup analysis until age 39, after which the final category was collapsed into “> 40 years” (Castori et al., 2011). Differences between age groups were analyzed using Kruskal-Wallis test for continuous variables and Pearson’s chi-square test for categorical variables.

**Aim 2**

The associations between personal, clinical, environmental, and HRQOL factors identified in Aim 1 were tested using chi-squared tests for categorical variables and Spearman’s rho test for continuous variables.
**Aim 3**

The primary outcomes for Aim 3 were physical and mental HRQOL, using SF-36 PCS to measure physical HRQOL and SF-36 MCS to measure mental HRQOL. Independent variables included sociodemographic, health history, symptom characteristics, and environmental factors. Because the data did not meet assumptions for multiple linear regression, Aim 3 was explored using non-parametric correlation analysis. Correlations between health outcomes and SF-36 PCS and MCS were analyzed using Spearman’s rank correlation coefficient, with effect sizes interpreted as < .40 = weak; .40 - .59 = moderate, and ≥ .60 = strong. Differences between the sample PCS and MCS means were compared with established U.S. norms using t-tests. Data were analyzed using SPSS version 29.0. Statistical tests were 2-tailed with a significance level of $p < .05$.

Free-text responses were analyzed by directed content analysis (Hsieh & Shannon, 2005). The researcher established the initial coding categories using the ICF domains and definitions as the deductive framework. Participants’ free-text responses were reviewed, and text corresponding to the framework categories was given initial codes. Codes were further subdivided into the One-Level ICF Classifications, which were then included in the final model, and illustrative quotes were selected that confirmed the descriptive and correlational data from the statistical analysis.

**Confounders**

Despite no restriction on study participation from international communities, the participant sample was homogeneous and overwhelmingly white, well-educated, and currently residing in the U.S., therefore analyses were not controlled for demographic variables.
Data Management

The investigator managed all research data on this study following the University of Missouri System’s Research Data Security policies and best practices (https://www.umsystem.edu/ums/is/infosec/research-data-security). All digital data was stored on secure servers at the University of Missouri, with backup to Microsoft OneDrive file hosting service (https://onedrive.live.com) as approved by the University of Missouri. Devices storing research data maintained up-to-date software and anti-virus patches. All paper research data was stored in a secure, locked location with access restricted to key personnel and supervised by the investigator. The investigator will retain all research records during the data collection period and for three subsequent years.

Threats to Validity

The researchers took steps to minimize threats to validity. Some risks of bias are inherent in an anonymous online survey (Artino et al., 2018; Mann, 2004; Choi & Pak, 2005). Using a non-random sample recruited from online support groups risks selection bias and may not represent all midlife and older women with hEDS/HSD. The self-reporting of historical health information risks recall bias. Health history and diagnoses cannot be verified without in-person interaction with participants. This study took measures to minimize non-response bias, such as making the questionnaire as short as possible and item responses as inclusive as possible. Nevertheless, there may have been differences between those who completed all items and those who did not. Validated questionnaires for symptoms, environmental factors, and HRQOL mitigated instrumentation bias. The study aimed for a sufficient sample size to justify parametric tests (Khorsan & Crawford, 2014; Bettany-Saltikov & Whittaker, 2013).
Study information, questionnaire item selection, wording, and results analysis were designed with cultural bias considerations in mind (Choi & Pak, 2005). Women of color or with few economic resources may not have had access to healthcare, the ability to take time off work, or request an accommodation for pain-related conditions. Therefore, the analysis controlled for race/ethnicity and employment status (Kuhlman et al., 2019). The survey was tested for readability and reviewed by the academic mentor and nursing school peers before commencing the study.

**Ethical Considerations**

**Protection of Human Subjects**

The researchers acknowledged their obligation to understand and adhere to laws and ethical guidelines for scientific research established by the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979) and committed to upholding nursing’s core values of honesty, dignity, and respect for human life (Milton, 2017). Recruitment and data collection commenced only after project approval from the University of Missouri Institutional Review Board. All participant data was deidentified before analysis and secured as outlined in section 3.4, Data Management. This study delivered no intervention, and participants were not compensated. No adverse events were anticipated, and any risk to participants was deemed no greater than the risk usually encountered in daily life. Any relationship between researchers and participants was unknown during the study. Although this study presented no direct benefits to participants, there was an important indirect benefit of contributing important knowledge about this under-researched population.
Recruitment and Informed Consent

Study recruitment through social media and support groups and established inclusion/exclusion criteria minimized the likelihood of recruiting individuals with diminished capacity for informed consent. Informed consent was indicated by a respondent selecting the "I agree" button on the online consent form, following the online screening criteria and detailed study description. Also, the researchers provided participants with contact information if they had questions or wanted further information. The online screens allowed the respondent to print the study description and consent form.

Inclusion of Women, Minorities, and Individuals Across the Lifespan

Due to this study’s nature and stated aims, the researchers limited participants to women aged 40 and older. This study did not target nor exclude participation by geographic location, race, or ethnicity. The global reach and anonymous nature of online EDS support groups hampered efforts to facilitate the inclusion of underrepresented groups. However, the researchers anticipated the results would be comparable to an analysis of an Ehlers-Danlos syndrome patient registry assembled by the National Institute on Aging (Schubart et al., 2019). This cohort of 175 patients (77.1% female) showed racial/ethnicity distribution as 85.7% White, 3.4% Hispanic, 0.6% Asian/Pacific Islander, 0.6% Black, and 9.7% Unknown/not reported. A recent feasibility study on older women with hEDS/HSD from a single Facebook group yielded 30 participants from the US, UK, Canada, and Switzerland, and all participants were White (Anderson & Lane, 2023).
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Chapter Six

Results

Health-related Quality of Life in Midlife and Older Women With Hypermobile
Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorders

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Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorders.
Manuscript submitted for publication.

Authorship Statement

The author confirms sole responsibility for the following: Study conception and design,
data collection, analysis and interpretation of results, and manuscript preparation.
Abstract

Introduction. Most researchers have studied health-related quality of life in hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders in young to middle-aged adults. This study aimed to identify factors associated with health-related quality of life in midlife and older women with this condition. Methods. Cross-sectional internet survey using the International Classification of Functioning, Disability and Health framework. Ethical Approval. The University’s institutional review board approved this study. Result. Current full or part-time employment, menopausal status, symptom severity, the ability to participate in social activities, the natural and built environment, and access to healthcare resources were associated with health-related quality of life in this population. Personal factors, including education level, number and types of comorbidities, response to therapies, and personal attitudes and outlook, also play a role in health-related quality of life in these women. Discussion. This study was the first to address midlife and older women with hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders and was the first to explore the environmental factors that influence health-related quality of life in these individuals. Conclusion. Future research should address the complex relationships among physical, social, personal, and environmental factors to maximize health-related quality of life in midlife and older women with hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders.

Keywords: Ehlers-Danlos syndrome, hypermobility spectrum disorders, joint instability, feasibility study, aging, older women, quality of life
Health-related Quality of Life in Midlife and Older Women with Hypermobile Ehlers-Danlos Syndrome and Hypermobility Spectrum Disorders

Hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders (hEDS/HSD) encompasses a group of heritable disorders characterized by joint hypermobility, tissue fragility, and chronic pain, with multisystemic manifestations that can lead to progressive disability and poor health-related quality of life (HRQOL; Castori et al., 2017; Tinkle et al., 2017). hEDS/HSD is poorly understood and frequently unrecognized despite an estimated prevalence of one in 500 adults (Demmler et al., 2019). hEDS/HSD appears to follow an autosomal dominant inheritance pattern, and adult females are more frequently and severely affected than males (Castori et al., 2010b). Because hEDS/HSD’s precise genetic basis remains unidentified, and the early symptoms are subtle and mimic other conditions, lengthy diagnosis delays are common (Kalisch et al., 2020). Most research into hEDS/HSD symptom progression has been conducted in samples with a mean age under 50 (Castori et al., 2010a; 2011; Copetti et al., 2019; Schubart et al., 2022).

Researchers know little about hEDS/HSD in older adults, so it is unclear how symptoms progress and whether diagnosis delays impact long-term health outcomes. Also, despite the greater prevalence and symptom severity in females, researchers do not know how hEDS/HSD symptoms manifest after menopause. Moreover, despite research suggesting the importance of supportive physical and social environments to individuals with hEDS/HSD (De Baets et al., 2017), specific environmental influences on hEDS/HSD require further investigation. Finally, although researchers have identified an association between hEDS/HSD and HRQOL (Berglund et al., 2015), there remains a
knowledge gap in the sociodemographic, clinical, and environmental factors associated with physical and mental HRQOL in midlife and older women with hEDS/HSD. Understanding these factors would facilitate earlier diagnosis and improve health outcomes in midlife and older women with hEDS/HSD.

A recent preliminary study determined that recruiting from EDS social media groups was feasible for an online survey to identify the clinical characteristics, symptom burden, and HRQOL in older women with hEDS/HSD (Anderson & Lane, 2023). Participants also suggested additional survey content, including more comorbid diagnoses, response to hormone replacement therapy, and information on surgical interventions and mobility aids including braces. These recommendations were included in the present survey. The baseline measurements from that feasibility study showing long diagnosis delays, multiple comorbidities, and poor health outcomes indicated the need to study the factors influencing HRQOL in midlife and older women with hEDS/HSD.

Aim

This cross-sectional internet survey aimed to identify factors associated with physical and mental HRQOL in midlife and older women with hEDS/HSD. The secondary aim was to provide an overview of sociodemographic features, clinical history, symptom characteristics, and environmental conditions associated with this population.

Methods

Theoretical Framework

The International Classification of Functioning, Disability and Health (ICF) provided the theoretical framework for this study (World Health Organization [WHO],
2001). The ICF is an international framework for designing and classifying health and health-related states (WHO, 2001). This framework is in two parts: Part One deals with functioning and disability, classified into two domains: (a) the body, including body functions and structures, and (b) activities and participation. Part Two deals with contextual factors that influence functioning, including (a) environmental and (b) personal characteristics. The ICF is a valuable framework for understanding complex disabling conditions, including hEDS/HSD (Jacobs et al., 2018; Scheper et al., 2016).

**Setting and Sample**

Data collection occurred between May 31 and June 30, 2023. The sample size of 64 was based on guidelines for the Short Form Health Survey (SF-36; Prieto et al., 1996). This size is sufficient to detect a 5-point score difference between the sample and a fixed norm, assuming 80% power, 2-tailed test, and \( p < .05 \). Survey eligibility criteria were:

- female
- age 40 or older
- able to read and understand English
- diagnosis of hEDS/HSD (or one of its previous diagnostic labels) by a licensed healthcare provider
- access to a computer with internet capability

The University Institutional Review Board approved this study, and all participants indicated their online consent before accessing the survey.

**Outcomes and Measures**

The primary outcomes were physical and mental HRQOL, measured by the SF-36 physical component summary (PCS) and mental component summary (MCS) scores
(Ware et al., 1994). The SF-36 is a 36-item self-report questionnaire developed by RAND as part of the Medical Outcomes Study that measures health status during the previous four weeks using Likert- and dichotomous responses (Ware & Sherbourne, 1992; Ware et al., 1993, 1994). The SF-36 organizes items into eight domains: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The PCS and MCS summary scores are derived from the domain scores. Age- and sex-stratified U.S. norms for the SF-36 domain and summary scores have been published (Ware et al., 1993, 1994). Each domain score and each summary score range from 0-100, with higher scores indicating better health status. The SF-36 summary scales have demonstrated good internal consistency and test-retest reliability (Ware et al., 1994). The SF-36 PCS and MCS measures are widely used in hEDS/HSD research to measure health outcomes (Bovet et al., 2016; Hakimi et al., 2020; Schubart et al., 2022). Physical and mental HRQOL were further explored using four optional free-text fields in the survey about the things that improved or reduced their physical and mental well-being. The survey also included an optional free-text field for participants to list any symptoms or comorbid diagnoses not covered in the survey instrument.

Secondary outcomes included sociodemographic features, clinical history, symptom characteristics, and environmental factors. Researchers designed a custom instrument to collect sociodemographic and clinical history. Symptom characteristics were measured using the Multidimensional Health Assessment Questionnaire (MDHAQ; Pincus et al., 1999). The MDHAQ is a multi-item, multi-format self-report questionnaire designed for rheumatology clinical assessment and research (Pincus, 2007; Pincus et al.,
The MDHAQ provides scale measures for function (FN), pain (PN), fatigue (FT), a 60-symptom review of systems (ROS), self-report of global health status (PATGL), and index measures, including the Routine Assessment of Patient Index Data 3 (RAPID3) and the Rheumatoid Arthritis Disease Activity Index (RADAI). Higher scores on the MDHAQ scale and index measures indicate worse health status. The MDHAQ has demonstrated good internal consistency (Leeb et al., 2009), test-retest reliability (Pincus et al., 1999), and criterion, content, and convergent validity (Josefsson, 2013; Pincus et al., 1999). The MDHAQ has been used in hEDS/HSD studies for its utility in musculoskeletal and multisystemic measures (Anderson & Lane, 2023; Palmer et al., 2016).

Environmental factors were measured using the Craig Hospital Inventory of Environmental Factors, short form (CHIEF-SF; Craig Hospital, 2001). The CHIEF-SF, derived from the full Craig Hospital Inventory of Environmental Factors (CHIEF), is a 12-item self-report questionnaire designed to measure the frequency and magnitude of environmental barriers encountered in the previous 12 months (Craig Hospital, 2001). Five subscale scores, including policies, physical/structural, work/school, attitudes/support, and services, are derived from the item scores. Each item score range is 0 - 8, and the instrument overall ranges from 0 - 96, with higher scores indicating more environmental barriers. The CHIEF has demonstrated good internal consistency and test-retest reliability (Whiteneck et al., 2004). The CHIEF-SF has been used to assess perceived environmental barriers in persons with stroke, traumatic brain injury, spinal cord injuries, and amputees (Carlsson et al., 2021; Ephraim et al., 2006; Heinemann et al., 2016) but has yet to be used in published hEDS/HSD studies.
Procedure

Links to study information were posted to EDS Facebook groups once approved by a site administrator. The link included study and researcher contact information, screening criteria, and a button to indicate consent. After consenting, participants were directed to the survey. Participants received no compensation for this study.

Statistical Analysis

Data were collected and managed using Research Electronic Data Capture (REDCap), a secure, web-based application that supports data capture, analysis, and audit trails for research studies (Harris et al., 2009). Participant responses were included in the analysis if complete enough to calculate outcomes of interest, and no data were imputed. Descriptive statistics were reported as means with standard deviations or medians with ranges for continuous variables and frequencies with percentages for categorical variables. Non-parametric tests were used with non-normally distributed variables. Correlations between health outcomes and SF-36 PCS and MCS were analyzed using Spearman’s rank correlation coefficient, with effect sizes interpreted as .10 = small, .30 = medium, and .50 = large (Field, 2018). Differences between the sample PCS and MCS means were compared with established U.S. norms using t-tests. Data were analyzed using SPSS version 29.0. Statistical tests were 2-tailed with a significance level of \( p < .05 \).

Free-text responses were analyzed by directed content analysis (Hsieh & Shannon, 2005). The researcher established the initial coding categories using the ICF domains and definitions as the deductive framework. Participants’ free-text responses were reviewed, and text corresponding to the framework categories was given initial
codes. Codes were further subdivided into the One-Level ICF Classifications, which were then included in the final model, and illustrative quotes were selected that confirmed the descriptive and correlational data from the statistical analysis.

**Results**

Ninety women accessed the eligibility screening, and 76 consented to participate in the study. Sixty-six participants, with a mean age of 55, completed all items necessary for calculating the health outcomes of interest. Table 6.1 shows the demographic characteristics of participants. Nearly all participants were White, current U.S. residents, college-educated, and married. An equal number of individuals were employed full-time or unemployed due to disability, and 20% were retired. Most individuals described their current ability as independent or mostly independent.

**Table 6.1**

_Demographic Characteristics of Participants_

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>n</th>
<th>M (SD)</th>
<th>Mdn (Range)</th>
<th>Freq (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>66</td>
<td>55.2 (10.4)</td>
<td>53.5 (40–87)</td>
<td></td>
</tr>
<tr>
<td>US resident</td>
<td>65</td>
<td></td>
<td></td>
<td>62 (95.4)</td>
</tr>
<tr>
<td>White race</td>
<td>65</td>
<td></td>
<td></td>
<td>62 (95.4)</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>65</td>
<td>16.8 (3.7)</td>
<td>17.0 (3–30)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>66</td>
<td></td>
<td></td>
<td>41 (62.1)</td>
</tr>
<tr>
<td>Employed full or part–time</td>
<td>66</td>
<td></td>
<td></td>
<td>24 (36.4)</td>
</tr>
<tr>
<td>Self–described independent or mostly</td>
<td>66</td>
<td></td>
<td></td>
<td>44 (67.7)</td>
</tr>
<tr>
<td>independent</td>
<td></td>
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</tbody>
</table>
Table 6.2 displays the participants’ health history and outcomes. The median age of hEDS/HSD symptom onset was six years (range one to 48 years), and the median age for seeking treatment was 25 (range one to 65). The median age for diagnosis was 47 (range eight to 68). Over 64% of participants were post-menopausal. Comorbid diagnoses were common, as shown in Figure 6.1. More than 50% of participants had a diagnosis of osteoarthritis, anxiety, temporomandibular joint dysfunction (TMJ), postural orthostatic tachycardia syndrome (POTS), depression, or gastroesophageal reflux disease (GERD). Nearly all (97%) participants reported two or more comorbidities, and over half (62.1%) reported seven or more comorbid diagnoses. Figure 6.2 shows current or past women’s health problems. Half of the participants reported painful menstrual periods (92.4%), urinary frequency (83.3%), painful sexual intercourse (81.5%), vaginal dryness (65.2%), and urinary incontinence (60.6%). Figure 6.3 shows the participants’ surgical history. Over 50% of participants reported laparoscopic or open abdominal procedures, or orthopedic procedures on upper or lower extremities.

Table 6.2

*Health History and Outcomes*

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>M (SD)</th>
<th>Mdn (Range)</th>
<th>Freq (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Health Characteristics</strong></td>
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</tr>
<tr>
<td>BMI</td>
<td>66</td>
<td>30.4 (7.9)</td>
<td>28.8 (18–51)</td>
<td></td>
</tr>
<tr>
<td>Age of symptom onset (yr)</td>
<td>65</td>
<td>7.6 (7.0)</td>
<td>6.0 (1–48)</td>
<td></td>
</tr>
<tr>
<td>Age sought treatment (yr)</td>
<td>63</td>
<td>27.2 (14.8)</td>
<td>25.0 (1–65)</td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis (yr)</td>
<td>64</td>
<td>45.9 (12.4)</td>
<td>47.0 (8–68)</td>
<td></td>
</tr>
<tr>
<td>Symptom/disease duration (yr)</td>
<td>63</td>
<td>38.3 (13.7)</td>
<td>38.0 (0–63)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>M (SD)</td>
<td>Mdn (Range)</td>
<td>Freq (%)</td>
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<tr>
<td>Sought treatment to diagnosis (yr)</td>
<td>61</td>
<td>18.4 (15.9)</td>
<td>18.0 (0–57)</td>
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</tr>
<tr>
<td>Undergone menopause (&gt; 1 year since LMP)</td>
<td>65</td>
<td></td>
<td></td>
<td>42 (64.6)</td>
</tr>
<tr>
<td>Age last menstrual period</td>
<td>41</td>
<td>45.3 (7.5)</td>
<td>48.0 (25–55)</td>
<td></td>
</tr>
<tr>
<td>Total # pregnancies</td>
<td>52</td>
<td>3.7 (2.4)</td>
<td>3.0 (1–12)</td>
<td></td>
</tr>
<tr>
<td>Total # live births</td>
<td>52</td>
<td>2.2 (1.4)</td>
<td>2.0 (0–6)</td>
<td></td>
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<tr>
<td>Total # comorbid diagnoses</td>
<td>66</td>
<td>7.2 (3.3)</td>
<td>7.0 (1–15)</td>
<td></td>
</tr>
<tr>
<td>≥ 2 comorbid diagnoses</td>
<td>66</td>
<td></td>
<td></td>
<td>64 (97.0)</td>
</tr>
<tr>
<td>≥ 7 comorbid diagnoses</td>
<td>66</td>
<td></td>
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<td>41 (62.1)</td>
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<tr>
<td>Total # surgical procedures</td>
<td>66</td>
<td>2.41 (2.1)</td>
<td>2.0 (0–10)</td>
<td></td>
</tr>
<tr>
<td>≥ 4 surgical procedures</td>
<td>66</td>
<td></td>
<td></td>
<td>14 (21.2)</td>
</tr>
<tr>
<td><strong>MDHAQ</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FN</td>
<td></td>
<td>3.1(1.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PN</td>
<td></td>
<td>6.6 (1.8)</td>
<td></td>
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<tr>
<td>FT</td>
<td></td>
<td>7.5 (2.2)</td>
<td></td>
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<tr>
<td>RADAi</td>
<td></td>
<td>19.2 (8.8)</td>
<td></td>
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</tr>
<tr>
<td>PATGL</td>
<td></td>
<td>6.1 (2.2)</td>
<td></td>
<td></td>
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<tr>
<td>RAPID3</td>
<td></td>
<td>15.9 (4.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ROS</td>
<td></td>
<td>24.9 (9.7)</td>
<td></td>
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<tr>
<td><strong>CHIEF-SF</strong></td>
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<td></td>
</tr>
<tr>
<td>Frequency</td>
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</tr>
<tr>
<td>Magnitude</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>n</td>
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<td>Mdn (Range)</td>
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<td>----------------</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td>1.9 (1.1)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Subscales</strong></td>
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<tr>
<td>Policies</td>
<td></td>
<td>1.8 (2.4)</td>
<td></td>
<td></td>
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<tr>
<td>Physical/Structural</td>
<td></td>
<td>3.7 (2.5)</td>
<td></td>
<td></td>
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<tr>
<td>Attitudes</td>
<td></td>
<td>1.6 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Services</td>
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<td>1.9 (1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SF-36</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Physical function</td>
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<td>35.6 (24.3)</td>
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<td></td>
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<tr>
<td>Role limitations - physical</td>
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<td>9.1 (20.4)</td>
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</tr>
<tr>
<td>Role limitations - emotional</td>
<td></td>
<td>42.4 (44.7)</td>
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</tr>
<tr>
<td>Vitality</td>
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<td>18.0 (16.5)</td>
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<td>Mental health</td>
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<td>Social functioning</td>
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<td>29.2 (24.6)</td>
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<td>Bodily pain</td>
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<td>General health</td>
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<td>PCS</td>
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<td>24.8 (7.8)</td>
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<td>MCS</td>
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<td>41.5 (11.2)</td>
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</table>

*Note.* BMI, body mass index; CHIEF-SF, Craig Hospital Inventory of Environmental Factors – Short Form; FN, functional status; FT, fatigue; LMP, last menstrual period; MCS, mental component summary; MDHAQ, Multidimensional Health Assessment
Questionnaire; PATGL, patient global health status; PCS, physical component summary; PN, pain; RAPID3, Routine Assessment of Patient Index Data 3, ROS, review of systems; SF-36, Short Form 36 Health Survey

Figure 6.1

Comorbid Diagnoses

Note. ASD, autism spectrum disorder; CFS/ME, chronic fatigue syndrome/myalgic encephalomyelitis; GERD, gastroesophageal reflux disorder; IBS, irritable bowel disorder; MVP, mitral valve prolapse; OA, osteoarthritis; POTS, postural orthostatic tachycardia syndrome; RA, rheumatoid arthritis; TMJ, temporal mandibular joint dysfunction.
Figure 6.2

Women’s Health History

![Women's Health History (n = 66)](chart)

Figure 6.3

Surgical Procedures

![Surgical Procedures (n = 66)](chart)

Note. Abdominal procedures include open and laparoscopic procedures. Lower extremity procedures include any procedure on the hip, knee, ankle, or foot. Upper extremity procedures include any procedure on the shoulder, arm, or hand.
Table 6.3 shows bivariate associations between independent variables and the SF-36 PCS and MCS. Being employed full or part-time ($r_s = .317, p = .009$) was positively associated with PCS. Being post-menopausal ($r_s = -.264, p = .034$) was negatively associated with PCS but was not associated with MCS. Comorbidities negatively associated with PCS included fibromyalgia ($r_s = -.303, p = .013$), osteopenia/osteoporosis ($r_s = -.270, p = .028$), GERD ($r_s = -.310, p = .011$), and total number of comorbidities ($r_s = -.321, p = .009$). Comorbidities negatively associated with MCS included anxiety ($r_s = -.273, p = .026$), depression ($r_s = -.393, p = .001$), and urinary frequency ($r_s = -.323, p = .008$). All subgroups of the MDHAQ except for ROS were significantly associated with PCS. The MDHAQ subgroups FT, PATGL, and ROS were significantly associated with MCS. CHIEF-SF frequency, magnitude, and total were all negatively associated with PCS and MCS. CHIEF-SF summary scores of policies, physical/structural, and services were negatively associated with PCS, and physical/structural, attitudes, and services were negatively associated with MCS. The CHIEF-SF school/work summary scale was omitted from the analysis due to the preponderance of older, retired participants.

Table 6.3

*SF-36 Physical and Mental Health Component Summary Bivariate Associations*

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<tr>
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<td>$r_s$</td>
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<td>$p$</td>
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<td>-.151</td>
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<td>Age sought treatment</td>
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<td>Age diagnosis</td>
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<td>Sought treatment to diagnosis</td>
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<td>duration (yr)</td>
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<td>Disease/symptom duration</td>
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<td>Urinary frequency</td>
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<td>-.161</td>
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<td>-.350</td>
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**CHIEF-SF**

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<td>Magnitude</td>
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<td>-.385</td>
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<td>Total</td>
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<td>-.573, -.143</td>
<td>.002**</td>
<td>-.445</td>
<td>-.624, -.220</td>
<td>&lt;.001***</td>
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Summary scores

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<td>Policies</td>
<td>-.278</td>
<td>-.493, -.031</td>
<td>.024*</td>
<td>-.224</td>
<td>-.448, .026</td>
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<td>Physical/Structural</td>
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<td>-.284</td>
<td>-.497, .037</td>
<td>.021*</td>
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<td>Attitudes</td>
<td>-.155</td>
<td>-.389, .097</td>
<td>.213</td>
<td>-.405</td>
<td>-.579, -.174</td>
<td>&lt;.001***</td>
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<td>Services</td>
<td>-.409</td>
<td>-.597, -.178</td>
<td>&lt;.001***</td>
<td>-.301</td>
<td>-.511, -.056</td>
<td>.014*</td>
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</tbody>
</table>

Notes. BMI, body mass index; CHIEF-SF, Craig Hospital Inventory of Environmental Factors - Short Form; FN, functional status; FT, fatigue; GERD, gastroesophageal reflux disorder; MCS, Mental Component Summary; MDHAQ, Multidimensional Health Assessment Questionnaire; PATGL, patient global health status; PCS, Physical Component Summary; PN, pain; RADAIR, Rheumatoid Arthritis Disease Activity Index; RAPID3, Routine Assessment of Patient Index Data 3; ROS, review of systems; SF-36, Short Form 36 Health Survey. Bivariate associations by Spearman’s rank correlation.

*p < .05

**p < .01
Table 6.4 compares the current PCS and MCS results with population norms published by Ware et al. (1994). Results indicated the participants had a significantly lower PCS score (M = 24.8, SD = 7.8) than the U.S. population age- and sex-based norms (M = 45.0, SD = 11.6), $t(65) = 21.1$, $p < .001$, $d = 2.6$. Similarly, participants also had a significantly worse MCS score (M = 41.5, SD = 11.2) than US population age- and sex-based norms (M = 50.5, SD = 10.2), $t(65) = 6.6$, $p < .001$, $d = 0.8$.

Table 6.4
Current Study SF-36 PCS and MCS: Comparison with U.S. Population Norms

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<tr>
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<th>Current Sample</th>
<th>U.S. norm (Ware et al., 1994)</th>
<th>$t$</th>
<th>$p$</th>
<th>$d$</th>
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<tr>
<td></td>
<td>n = 66 (mean age 55.2, 100% female)</td>
<td>n = 193 (age 45-54, 100% female)</td>
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</tr>
<tr>
<td></td>
<td>M (SD)</td>
<td>M (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCS</td>
<td>24.8 (7.8)</td>
<td>45.0 (11.6)</td>
<td>−21.16</td>
<td>&lt;.001</td>
<td>−2.600</td>
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<tr>
<td>MCS</td>
<td>41.5 (11.2)</td>
<td>50.5 (10.2)</td>
<td>−6.60</td>
<td>&lt;.001</td>
<td>−0.813</td>
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</tbody>
</table>

Note. MCS, mental component summary; PCS, physical component summary

Table 6.5 shows participants’ free-text responses about what improves or reduces their well-being, with illustrative quotes categorized into ICF categories. Physical and mental HRQOL were decreased by poorly managed symptoms, including pain, fatigue, brain fog, and poor sleep. Activity limitations, weather factors, and barriers to healthcare resources also reduced HRQOL. Participant comments indicated HRQOL was improved by rest, well-managed symptoms, supportive social interactions, good weather, and
positive interactions with healthcare providers. Comorbidities, restrictions to treatments, and personal attitudes and outlook also impacted HRQOL. Figure 6.4 shows the proposed ICF model of factors impacting HRQOL in midlife and older women with hEDS/HSD identified in this study’s quantitative and qualitative findings.

Table 6.5

Qualitative Responses Regarding HRQOL in Midlife and Older Women with hEDS/HSD

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<th>Free text questions</th>
<th>n</th>
<th>Illustrative Quotes/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1. What types of things improve your physical well-being?</td>
<td>45</td>
<td><strong>Body Functions and Structures</strong>&lt;br&gt;“Feel better when no brain fog” (Participant 11, age 71)&lt;br&gt;“Pain relief, and getting good sleep” (Participant 38, age 46)&lt;br&gt;“Getting enough sleep” (Participant 78, age 52)&lt;br&gt;<strong>Activities and Participation</strong>&lt;br&gt;“Getting outside and swimming in the pool” (Participant 18, age 45)&lt;br&gt;“Being able to do things I enjoy - watercolor painting, very light gardening, crochet, baking” (Participant 72, age 47)&lt;br&gt;<strong>Environment</strong>&lt;br&gt;“Perfect temperature 70 degrees no humidity” (Participant 11, age 71)&lt;br&gt;“Myofascial body work – unfortunately not covered by Medicare so I can’t do it as often as I would like. But it definitely helps!” (Participant 83, age 66)&lt;br&gt;<strong>Personal</strong>&lt;br&gt;“Rather than just medicate, I try to find a long-lasting solution – whether it be PT or a surgery” (Participant 15, age 60)</td>
</tr>
<tr>
<td>Free text questions</td>
<td>n</td>
<td>Illustrative Quotes/Comments</td>
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<tr>
<td>---------------------</td>
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</tbody>
</table>
| Q2. What types of things reduce your physical well-being? | 50 | **Body Functions and Structures**

- “Fatigue, brain fog, pain, lack of sleep…” (Participant 11, age 71)
- “Pain, nothing is working to treat symptoms” (Participant 47, age 42)

**Activities and Participation**

- “Being unable to do the things I want and need to do physically or socially” (Participant 50, age 43)
- “Sitting in uncomfortable chairs, standing in one spot, not being able to rest my head, things out of reach, inability to stretch” (Participant 70, age 63)

**Environment**

- “Having to wait on Dr. appointments hinders me greatly because I can’t move forward, and am not sure which approach to take” (Participant 15, age 60)
- “Stormy weather & barometer changes” (Participant 42, age 55)
- “Noise, bright lights, strong smells like perfume and air freshener” (Participant 41, age 49)

**Personal**

- “Hyperfocusing on what I cannot do” (Participant 17, age 56)
- “Overdoing it (ignoring my limits)” (Participant 23, age 40)
- “Taking care of elderly mother” (Participant 32, age 48)
- “Physically caring for my elderly father” (Participant 58, age 65)
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<th>Illustrative Quotes/Comments</th>
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<td>Q3. What types of</td>
<td>47</td>
<td><strong>Body Functions and Structures</strong></td>
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<tr>
<td>things improve your</td>
<td></td>
<td>“Getting plenty of rest” (Participant 36, age 63)</td>
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<tr>
<td>mental well-being?</td>
<td></td>
<td>“Lack of pain, ability to move” (Participant 50, age 43)</td>
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<td>“Well-managed EDS symptoms” (Participant 59, age 72)</td>
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<td><em>Activities and Participation</em></td>
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<td>“Social activities within my bodies [sic] capabilities with people</td>
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<td></td>
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<td>who get my limitations.” (Participant 44, age 40)</td>
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<td></td>
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<td>“Being with friends and family who bring me joy” (Participant 54,</td>
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<td></td>
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<td>age 62)</td>
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<td><em>Environment</em></td>
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<td></td>
<td></td>
<td>“Support and encouragement from docs and physical therapist”</td>
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<td></td>
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<td>(Participant 23, age 40)</td>
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<td></td>
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<td>“Cool breezes, sunny days” (Participant 70, age 63)</td>
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<td></td>
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<td>“Focus on positive, help others and keep my mind busy on other</td>
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<td>things” (Participant 2, age 68)</td>
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<td>“Being thankful” (Participant 17, age 56)</td>
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<td>Q4. What types of</td>
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<td><strong>Body Functions and Structures</strong></td>
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<td>things reduce your</td>
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<td>“No energy ever, everything I do is difficult because I lack energy</td>
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<td>mental well-being?</td>
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<td>which makes me very frustrated” (Participant 1, age 57)</td>
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<td></td>
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<td>“Pain and fatigue” (Participant 45, age 54)</td>
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<tr>
<td>Free text questions</td>
<td>n</td>
<td>Illustrative Quotes/Comments</td>
</tr>
<tr>
<td>---------------------</td>
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</tr>
<tr>
<td>“Increased sustained pain, interrupted sleep due to subluxations and pain” (Participant 72, age 47)</td>
<td></td>
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</tr>
</tbody>
</table>

**Activities and Participation**

“Limitations. I have had to depend on help from my family for much of the year this year … I would like to be able to accomplish things on my own.” (Participant 15, age 60)

“Having to bail on people when body isn’t cooperating” (Participant 23, age 40)

“Being stuck at home, not being able to participate in my community” (Participant 41, age 49)

**Environment**

“Medical gaslighting, not being able to find knowledgeable EDS informed doctors” (Participant 50, age 43)

“Barriers to healthcare – access to knowledgeable physicians/providers, insurance limits on medications/treatments, mistreatment by physicians (medical PTSD), poor medical records” (Participant 77, age 51)

**Personal**

“No hope for improvement” (Participant 11, age 71)

“Being negative, hyper, focusing on my inabilities” (Participant 17, age 56)

“Being alone” (Participant 23, age 40)

“Worrying about the future for my daughter and grandsons” (Participant 54, age 62)
Figure 6.4

ICF Model of Factors Impacting HRQOL in Midlife and Older Women With hEDS/HSD

**Body Functions and Structures**
- Impairments
  - Mental functions
    - Brain fog
    - Poor sleep
    - Depression
  - Sensory functions and pain
    - Chronic pain
    - Functions of cardiovascular and respiratory systems
    - Poor exercise tolerance
    - Chronic fatigue
    - Autonomic instability
    - Genitourinary and reproductive functions
    - Urinary frequency
    - Menopausal status
    - Neurovascular and movement functions
    - Joint instability/injuries
    - Loss of muscle mass

**Activities and Participation**
- Abilities
  - Self-care
    - Diet management
    - Gentle exercise
    - Rest
  - Managing complex health regimens
  - Interpersonal interactions and relationships
    - Supportive family relationships
    - Major life areas
    - Full- or part-time employment
    - Community, social, and civic life
    - Hobbies
    - Faith activities

**Environmental Factors**
- Facilitators
  - Products and Technology
    - Mobility devices
    - Safe, aging-in-place home
    - Gentle outdoor activities/getting out in nature
  - Support and relationships
    - Supportive family and friends
    - Knowledgeable and supportive healthcare providers
    - Services, systems and policies
    - Access to consistent and timely healthcare

- Natural environment
  - Weather
  - Light, sound, odors
  - Support and relationships
  - Lack of EDS-knowledgeable healthcare providers
  - Services, systems and policies
  - Insurance restrictions
  - Bureaucratic health systems

**Personal Factors**
- Limitations/Restrictions
  - General tasks and demands
  - Difficulties carrying out daily routine
  - Difficulties handling stress
  - Domestic life
  - Difficulties managing household tasks
  - Caring for elderly family members
  - Interpersonal interactions and relationships
  - Difficulty maintaining interpersonal relationships
  - Major life areas
  - Economic stress
  - Community, social and civic life
  - Difficulty participating in social activities

**hEDS/HSD in Older Women**

*Note.* EDS, Ehlers-Danlos syndromes; hEDS/HSD, hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders; ICF, International Classification of Functioning, Disability and Health.
Discussion

This study is the first to comprehensively describe the clinical characteristics, health outcomes, and physical and mental HRQOL in midlife and older women with hEDS/HSD. Previous studies show that hEDS/HSD symptoms begin in childhood, and diagnosis may be delayed for many years (Castori et al., 2011; Kalisch et al., 2020). This study found no significant association between HRQOL and temporal factors, including current age, age of symptom onset, age of diagnosis, length of diagnosis delay, or disease/symptom duration. This result contrasts with other studies that found HRQOL associations with age (Avis et al., 2018; Wysocka-Skurska et al., 2016) and disease duration (Wysocka-Skurska et al., 2016). This relationship between temporal factors and health outcomes needs to be further investigated to determine if health outcomes are influenced by access to evidence-based, multidisciplinary care coordinated by an EDS-knowledgeable provider after diagnosis.

Results from this study are consistent with other research regarding factors influencing HRQOL in midlife and older women, including the number and type of comorbid conditions (Avis et al., 2018), menopausal status (Avis et al., 2018), and pain (Wysocka-Skurska et al., 2016). This study also demonstrated that full or part-time employment was associated with HRQOL, echoing results from other studies about hEDS/HSD and other chronic conditions (De Baets et al., 2019; Fernández et al., 2011; Palomo-Toucedo et al., 2020). The implications of employment on healthcare access and work-based health insurance can severely impact women’s HRQOL. More research is needed to discern what aspects of employment (e.g., type of work, workplace culture,
accommodations) are the most influential in HRQOL. This information will aid career planning in working-aged individuals diagnosed with hEDS/HSD.

The participants’ narrative responses also highlight an issue with this population, as midlife and older women with hEDS/HSD face increasing symptoms and declining function, often while they are still employed and dealing with added responsibilities for the care of others, particularly midlife and older parents. The impact of hEDS/HSD in this group of women has not been explored.

This study is the first to examine environmental factors associated with HRQOL in this population. Results from the CHIEF-SF and the free-text responses from participants indicate HRQOL is impacted by the natural and built environment, policies, and service availability that impact access to knowledgeable healthcare providers and treatments. These results are consistent with prior studies that found that environmental factors, including physical surroundings, societal attitudes, and access to services, can be facilitators or barriers to HRQOL in individuals with chronic conditions (Abdi et al., 2019; De Baets et al., 2017).

This study has limitations. The sample’s demographic homogeneity limited its generalizability to other populations. The study design limited the participants to those who were knowledgeable about hEDS/HSD in that they were already diagnosed and were current participants in online support groups. Internet recruitment and self-reported survey measures precluded any ability to conduct corroborating physical exams and clinical history reviews. The survey addressed symptoms broadly, making it impossible to determine symptom characteristics and age of onset. Finally, results must be viewed cautiously due to the observational design and relatively small sample size.
Despite the limitations, this study has clinical and research implications. Not all participants reported routine access to specialty providers and treatments, but all participants had routine (e.g., at least annual) evaluations by primary care providers. This finding points to the need to include primary care providers in establishing research and treatment protocols for individuals with hEDS/HSD to ensure equitable access to care and practical, evidence-based diagnosis and treatment. Also, despite several hEDS/HSD studies using the ICF framework, none have to date examined the environmental influences on health outcomes in this population. More research is needed to untangle the complex relationships among environmental factors and symptoms historically attributed to poor HRQOL in hEDS/HSD, such as depression, fatigue, and pain.

**Conclusion**

This study identified physical, social, environmental, and personal factors associated with physical and mental HRQOL in midlife and older women with hEDS/HSD. This research also yielded a broad description of this population’s sociodemographic attributes, clinical history, symptom characteristics, and environmental features. More research is needed to explore the clinical trajectory and effective symptom management for midlife and older women with hEDS/HSD.
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Chapter Seven

Discussion

This study aimed to comprehensively understand hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders (hEDS/HSD) in midlife and older women and identify factors associated with health-related quality of life (HRQOL) in this population. This research produced a database of sociodemographic, clinical history, and health outcomes in this population that can serve as a jumping-off point for additional research about hEDS/HSD in midlife and older women.

Illustrative Case Study

The following case study of one participant illustrates the issues confronting midlife and older women with hEDS/HSD. Ms. A. is a 65-year-old woman who is married, retired, lives with her husband, and describes herself as mostly housebound. She experienced her first symptoms of joint pain as a young child and sought medical evaluation at age 30. Many years of healthcare encounters for multisystemic symptoms produced numerous comorbid diagnoses, including chronic fatigue syndrome, osteoarthritis, irritable bowel syndrome, pelvic organ prolapse, gastroesophageal reflux disorder, temporomandibular joint disorder, postural orthostatic tachycardia syndrome, sleep apnea, anxiety, and depression. Ms. A. also describes a history of painful sexual intercourse, vaginal dryness, and urinary frequency. She uses a cane and a wheelchair part-time. A referral to a geneticist in 2017 led to a diagnosis of hEDS at age 59, a delay of 50 years between symptom onset and diagnosis.

The convoluted and chaotic history of medicine’s understanding of symptomatic hypermobility disorders has impacted the experiences of midlife and older women with
hEDS/HSD. As described in Chapter Two, hEDS/HSD diagnosis delays result from disease, patient, provider, and system factors. The prevailing opinion in rheumatology and pediatrics during the 1960s to 1980s, the years when these participants might have undergone pediatric evaluation, was that generalized familial ligamentous laxity represented the extreme end of the normal variation in joint mobility, was common in children and that reports of musculoskeletal pain were infrequent, mild and self-limiting (Kirk et al., 1967; Klemp, 1997). Such pain would have been deemed benign or somatic without an apparent injury or confirmatory test. Pediatric chronic pain syndromes were assumed to be associated with psychological stressors such as school avoidance, divorce, or loss of loved ones (Gedalia et al., 1996). Upon recognizing that symptomatic hypermobility was more common in young females, some rheumatologists suggested psychological issues were a factor in symptom perpetuation, particularly in girls, “a group also especially susceptible to psychogenic limb pain” (Lewkonia & Ansell, 1983, p. 991).

From the 1960s through the 1980s, symptoms in children not easily explained by clinical evaluation were often labeled as a functional illness (De Leon, 1961; Thompson & Sills, 1988). Participants in this study, when they were children or young adults, were likely exposed to clinicians who judged their problems as psychosomatic, hysterical, or delusional. Providers and parents may have accused these participants of using their symptoms to gain attention or avoid unpleasant situations (De Leon, 1961). These experiences may have led to healthcare avoidance in adulthood, further delaying diagnosis. Thus, disease, patient, and provider factors would have been implicated in this extensive diagnosis delay.
System factors were also implicated in Ms. A.’s long delay in diagnosis. Case studies about individuals with symptomatic joint hypermobility were starting to be published in genetics literature in the early 1970s (Beighton & Horan, 1970). Pediatric geneticists focused on children with dysmorphic features or developmental delays, situations that might indicate a need for prenatal counseling (Lowry, 1988). The co-occurrence of orthostatic intolerance, chronic fatigue syndrome, and Ehlers-Danlos syndrome (EDS) was not identified among pediatricians until the late 1990s (Rowe et al., 1999). At this point, these study participants were no longer seeing pediatricians, and the perceptions of their multisystem dysfunction depended on the research and attitudes of specific disciplines and care providers. It remained unlikely they would be referred for genetic evaluation due to poor knowledge about hEDS/HSD among clinicians and the limited number of geneticists in adult medicine (Gay et al., 2019).

Nevertheless, Ms. A. finally received an hEDS/HSD diagnosis in her late 50s. An individual’s relief at finally receiving an hEDS/HSD diagnosis may be short-lived upon finding how little is known about its prognosis and effective treatment options. As shown in Chapter Three, there is almost no empirical research about the age-related trajectory of hEDS/HSD in older adults. Most hEDS/HSD natural history studies have been conducted in younger adults, and the few studies that discussed age-related hEDS/HSD outcomes found that symptom progression was multisystemic and unpredictable. The clinical problems Ms. A. accumulated over time were frequently found in adults with hEDS/HSD including chronic fatigue (Bénistan & Martinez, 2019; Bergl et al., 2019; Murray et al., 2013; Schubart et al., 2019, 2022), gastrointestinal problems (Alomari et al., 2020; Bergl et al., 2019), depression and anxiety (Murray et al., 2013), pelvic floor dysfunction (Bergl et al., 2019), etc.
et al., 2019; Glayzer et al., 2021; Hugon-Rodin et al., 2016), and autonomic dysfunction (Bergl et al., 2019; De Wandele et al., 2014). Ms. A.’s encounters with multiple specialty providers operating within disciplinary silos led to a health record full of assorted diagnoses with no provider who could see the big picture.

Individuals who received system-specific specialty care from proponents of the biopsychosocial (BPS) model were unlikely to receive more knowledgeable or coordinated care for their hEDS/HSD issues. The BPS model holds that individuals exist within a system of biological, social, and psychological factors and was proposed by Engel (1980) to replace the reductionist, traditional biomedical model. However, contemporary healthcare systems are designed to treat complex conditions in a compartmentalized fashion, allowing for wide variations in practice. This can result in frustration for both patients and providers.

After her diagnosis, and with little follow-up or guidance from healthcare providers, Ms. A sought information about her condition online. Through social media, she found groups of individuals with hEDS/HSD that gave her a sense of community and provided informal recommendations for activities and resources for symptom management (Ashtari & Taylor, 2022). However, individuals with hEDS/HSD have difficulty finding online trusted sources and evaluating the veracity of recommendations (Ashtari & Taylor, 2022). Discussing their online findings with providers is not always received well. A participant in a recent qualitative study about hEDS/HSD was told by their provider that EDS was “a fad made up of bored stay at home moms on facebook who want to be sick” (Estrella & Frazier, 2023, p.5). Such attitudes can lead to further medical avoidance, thus delaying both diagnosis and treatment.
Social media groups for rare or poorly understood conditions may be the only source of clinical information patients receive, which may explain their popularity with individuals with hEDS/HSD. These groups become potential recruitment pools for hEDS/HSD research. Chapter Four found that individuals in hEDS/HSD social media groups were willing and eager to support and participate in online surveys, making such research feasible for understanding hEDS/HSD in midlife and older women.

Chapters Five and Six detailed the methods and results of an online research study on HRQOL in midlife and older women with hEDS/HSD that used these social media communities as recruitment pools. The results were organized within the International Classification of Functioning, Disability and Health (ICF) framework (World Health Organization, 2001). This framework allows factors related to HRQOL in hEDS/HSD to be categorized as body functions and structures, activities and participation, environmental factors, and personal factors. In the case of Ms. A., body functions and structural factors that impacted her HRQOL included the physical symptoms of chronic fatigue, gastrointestinal dysfunction, arthritis pain, anxiety, and depression. Activities and participation factors included her interactions with friends and loved ones and her ability to engage in satisfying hobbies, including working with plants and journaling. Environmental factors included her ability to interact with the environment through nature walks and walking her dog. Environmental factors also included financial stress, dealing with the healthcare system through doctors’ appointments, medical tests, and handling insurance issues. Personal factors impacting her HRQOL included the number and severity of her comorbidities, response to medications and treatments, and physically caring for her elderly father. These influences were repeated often among participants in
this study, making Ms. A. a clear example of factors that impact HRQOL in this sample of midlife and older women with hEDS/HSD.

**Limitations**

**Positionality**

This research has limitations and several sources of potential bias. One possible source relates to the researcher’s positionality, which can influence both quantitative and qualitative studies (Berger, 2015; Jafar, 2018). A researcher’s shared experience with participants facilitates recruitment and content expertise but may provide a biased lens through which the researcher organizes, collects, and interprets data (Råheim et al., 2016). Insider researchers may struggle to maintain an open mind and the ability to consider alternate theories and methods or may inadvertently push a personal agenda regarding the research topic (Råheim, 2018). An insider positionality can lead to blurred boundaries, loss of objectivity, and questionable validity or trustworthiness of the findings (Berger, 2015; Råheim, 2018). For this reason, the details about the researcher’s insider role must be acknowledged and managed.

As an insider principal investigator, I share experiences with this study’s participants, including age group, gender, and diagnosis of hEDS/HSD. Furthermore, I share many medical and social experiences with the participants, including multiple healthcare encounters, surgeries, decades-long diagnosis delays, reduced function, and often poor health-related quality of life. Moreover, I share the experience of having symptoms ignored, discounted, and attributed to somatic factors for many years. Finally, I share the experience of the condition’s relentless progression with no known treatments to reverse or slow the disease outcome.
My role as an insider to the world of midlife and older women with hEDS/HSD has reduced certain barriers to research in this population. First, my insider position gives me more knowledge of the problems relevant to this study population, enhancing my ability to articulate comprehensive research questions and propose hypotheses (Berger, 2015). Second, my insider position allows me access to participant recruitment pools, such as support groups and social media sites (Berger, 2015). Third, the shared experiences between myself as the researcher and the study participants enable me to better appreciate the nuances in participants’ responses (Berger, 2015).

My role as a healthcare provider, a group historically responsible for discounting or disbelieving the experiences of individuals with hEDS/HSD, adds complexity to my positionality. I am also a member of an EDS research community affiliated with the International Consortium on the Ehlers-Danlos syndromes and am privy to cutting-edge discussions and preliminary study results not yet released to the public. Finally, I have a particular theoretical stance regarding hEDS/HSD as a condition with unknown but multifaceted etiology involving genetics, environmental stressors, infectious processes, and psychological influences. I also believe this condition’s physiological manifestations can sometimes mimic psychological pathology, with the precise relationship between physiological and psychological factors currently unclear. This theoretical stance is consistent with that held by the International Consortium. I acknowledge these aspects of my positionality likely influenced questionnaire topic selection, research instrument choice, and results interpretation.

With the assistance of my advisor, I managed these potential sources of bias through reflexivity and peer review. I have been upfront about having hEDS/HSD and
I have made no attempts to hide my diagnosis or its progression. I have actively participated in the closed and closely monitored Facebook groups from which I recruited participants. I have had monthly discussions with my advisor about the progress of my research, disability, and aging in general. Despite these efforts to manage potential bias, the results of this research should be viewed with my insider positionality in mind.

**Other Sources of Bias**

Some risks of bias are inherent in an anonymous online survey (Artino et al., 2018; Mann, 2004; Choi & Pak, 2005). Using a non-random sample recruited from online support groups risks selection bias and may not represent all midlife and older women with hEDS/HSD. The self-reporting of historical health information risks recall bias. Health history and diagnoses cannot be verified without record review or in-person interaction with participants. This study took measures to minimize non-response bias, such as making the questionnaire as short and item responses as inclusive as possible. Nevertheless, there may have been differences between those who completed all items and those who did not. Validated questionnaires for symptoms, environmental factors, and HRQOL mitigated instrumentation bias. Study information, questionnaire item selection, wording, and results analysis were designed with cultural bias considerations in mind (Choi & Pak, 2005). The survey was tested for readability and reviewed by my advisor and nursing school peers before commencing the study.

**Implications**

**Implications for Practice and Research**

The example of hEDS/HSD leads to the inescapable conclusion that the existing paradigms of medical care are insufficient to meet the demands of poorly understood,
multisystemic, chronic, and progressive conditions. Researchers and clinicians view the symptoms of hEDS/HSD through the lens of their discipline-specific specialties. Few primary care providers have knowledge or expertise in diagnosing or managing connective tissue disorders. They are therefore unlikely to suspect a connective tissue disorder as etiology for multimorbidity, particularly in midlife and older women.

Referrals to specialties are organ or system-specific, e.g., orthopedics for musculoskeletal problems, gastroenterology for gastrointestinal issues, cardiology or neurology for autonomic symptoms, and psychiatry for depression, or anxiety. This fragmentation of services highlights the need for a knowledgeable clinician to coordinate the care team and oversee the process of evaluation and treatment of individuals with complex, multisystem disorders such as hEDS/HSD.

Providers with little knowledge of multisystemic connective tissue disorders may attribute the plethora of symptoms to a somatic or functional disorder. Individuals with hEDS/HSD who present with multimorbidity are often assumed to have a psychiatric basis for their symptoms, mainly since few other modern medical paradigms account for a single etiology for multisystemic symptoms with no confirmatory biomarker (Hamonet et al., 2015). This assumption of a psychiatric cause is especially true if the individual acknowledges anxiety or depression despite this being a common reaction to a progressive, painful, poorly understood disorder.

This study also yielded recommended avenues for further research into hEDS/HSD in midlife and older women. Some research questions included:
• Is there a symptom profile in midlife and older women with undiagnosed hEDS/HSD that may trigger a provider’s index of suspicion for a connective tissue disorder, prompting further investigation leading to earlier diagnosis?
• Is there evidence that women aging with hEDS/HSD should expect poor and worsening health outcomes? If so, what steps might younger women with hEDS/HSD take to optimize their HRQOL in later life?
• How do we understand the comorbidities in midlife and older women with hEDS/HSD as they age? Are they expected outcomes related to aging, or are they manifestations of disordered connective tissue fundamentally different from these comorbidities in patients without hEDS/HSD?
• What changes are needed in the existing healthcare system to facilitate the creation of referral pathways for multidisciplinary treatment for hEDS/HSD?
• What is nursing’s role in identifying and caring for individuals, particularly midlife and older women, who present with known or suspected hEDS/HSD?

Implications for Policy

As the existing health and medical care paradigms must evolve to deal with the complexities of hEDS/HSD in midlife and older women, so does the current policy and regulatory environment. The quest for a hEDS/HSD biomarker to facilitate diagnosis, the central focus of most hEDS/HSD research, may have unintended consequences for the accessibility and use of genetic information. In the U.S., federal law prohibits genetic information from being used in health insurance and employment (Genetic Information Nondiscrimination Act of 2008). However, the statute is silent on using genetic data in other types of insurance, including long-term care, disability, and life insurance. The
legal status of using genetic data for these purposes is left to state statutes, which vary widely (National Human Genome Research Institute, 2023).

Aligning health systems, payers, and providers depends on understanding how primary and specialty care providers are used by individuals with complex, multimorbid, and undiagnosed conditions such as hEDS/HSD (Bynum et al., 2017). Because hEDS/HSD-knowledgeable providers are hard to find, patients may seek evaluation and treatment outside their approved payer networks. Such out-of-network visits can result in healthcare disparities based on access to private funding, transportation, and employment leave for multiple, lengthy provider visits.

Chronically ill, multimorbid, and complex patients have greater healthcare service usage, resulting in a higher socioeconomic burden and cost of illness (Angelis et al., 2015; Fryer et al., 2017). Clear, well-disseminated diagnostic and treatment guidelines implemented in an integrated fashion would reduce unnecessary and unhelpful specialty visits, as occurs when patients with rare disorders must research, initiate, and coordinate their own care (Fryer et al., 2017).

There are policy implications regarding reproductive options in individuals with hEDS/HSD. In this study, seven participants were pregnant at the time of the survey. Pregnancy may present a dilemma to individuals with hEDS/HSD, given the autosomal dominant transmission and wide phenotypic variability in the condition’s severity (Jacobs et al., 2018). Additionally, midlife women with hEDS/HSD who become pregnant face an increased risk of advanced age-related pregnancy and neonatal complications. These reproductive issues are now occurring in a bewildering and shifting legislative environment where care decisions may be politicized, with access to some reproductive
options in the U.S. primarily determined by the individual’s state of residence (Czarnecki et al., 2023).

**Implications for Nursing**

Nurses were the first to identify the association between EDS and HRQOL (Berglund et al., 2015). Nevertheless, as hEDS/HSD has no explicit disciplinary home, nursing’s role is similarly unclear. Nurses are not conceptually bound to organ or system-specific explanations for health challenges. They are uniquely positioned to operate across disciplinary silos and can help coordinate multidisciplinary evaluation and treatment. Nursing’s role in caring for individuals with hEDS/HSD is becoming recognized in some recently established EDS clinics, where they are members of the core care team for each patient, triage patient visits, and participate in research and educational activities (Knight et al., 2022). Furthermore, efforts are underway to establish a theoretical framework to advance a nursing specialty that would integrate nursing with genetics and genomics (Hu et al., 2018). Despite these efforts, based on current research, nursing remains underrepresented in EDS clinical and research endeavors.

**Conclusion**

This study reveals the need for more research on hEDS/HSD in midlife and older women. At the same time, nurses should become knowledgeable about hEDS/HSD and look for opportunities to advance nursing’s presence in the EDS clinical and research communities. Broad research initiatives include understanding the characteristics of hEDS/HSD in midlife and older women, identifying the long-term impact of hEDS/HSD on HRQOL in this population, and the application of nursing theories to inform research
and practice on rare, chronic, poorly understood, and highly disabling conditions such as hEDS/HSD.
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with Ehlers-Danlos syndromes: Results of a national cohort study on 134 patients.

*PLoS One*, 8(11), Article e80321. https://doi.org/10.1371/journal.pone.0080321
Appendix A. Institutional Review Board Approval

March 23, 2022

Principal Investigator: Linda Anderson (MU-Student)
Department: Nursing-PHD

Your IRB Application to project entitled Hypermobility Ehlers-Danlos Syndrome/Hypermobility Spectrum Disorders in Older Women: A Feasibility Study was reviewed and approved by the MU Institutional Review Board according to the terms and conditions described below:

<table>
<thead>
<tr>
<th>IRB Project Number</th>
<th>2090562</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB Review Number</td>
<td>374981</td>
</tr>
<tr>
<td>Initial Application Approval Date</td>
<td>March 23, 2022</td>
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<tr>
<td>Expiration Date</td>
<td>March 23, 2023</td>
</tr>
<tr>
<td>Level of Review</td>
<td>Exempt</td>
</tr>
<tr>
<td>Project Status</td>
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</tr>
<tr>
<td>Exempt Categories (Revised Common Rule)</td>
<td>45 CFR 46.104d(2)(i)</td>
</tr>
<tr>
<td>Risk Level</td>
<td>Minimal Risk</td>
</tr>
<tr>
<td>HIPAA Category</td>
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</tr>
<tr>
<td>Approved Documents</td>
<td>Informed Consent &amp; Assent - Consent (Exempt Studies Only): #588079, Other Study Documents - Instruments (i.e. surveys): #586621, Recruitment Materials - Recruitment Materials: #688083</td>
</tr>
</tbody>
</table>

The principal investigator (PI) is responsible for all aspects and conduct of this study. The PI must comply with the following conditions of the approval:

• No subjects may be involved in any study procedure prior to the IRB approval date or after the expiration date.
• All changes must be IRB approved prior to implementation utilizing the Exempt Amendment Form.
• Major noncompliance deviations must be reported to the MU IRB on the Event Report within 5 business days of the research team becoming aware of the deviation. Major deviations result when research activities may affected the research subject's rights, safety, and/or welfare, or may have had the potential to impact even if no actual harm occurred. Please refer to the MU IRB Noncompliance policy for additional details.
• The Annual Exempt Form must be submitted to the IRB for review and approval at least 30 days prior to the project expiration date to keep the study active or to close it.
• Maintain all research records for a period of seven years from the project completion date.

If you are offering subject payments and would like more information about research participant payments, please click here to view the MU Business Policy and Procedure: http://hppm.missouri.edu/chapter2/2.250.html

If you have any questions or concerns, please contact the MU IRB Office at 573-882-3181 or email to muresearch@missouri.edu.

Thank you,
MU Institutional Review Board
Appendix B. Institutional Review Board Exempt Amendment Form

Institutional Review Board
University of Missouri-Columbia
FWA Number: 00002876
IRB Registration Numbers: 00000731, 00009014
310 Jesse Hall
Columbia, MO 65211
573-882-3181
irb@missouri.edu

May 02, 2023

Principal Investigator: Linda Anderson (MU-Student)
Department: Nursing-PHD

Your Exempt Amendment Form to project entitled Hypermobile Ehlers-Danlos Syndrome/ Hypermobility Spectrum Disorders in Older Women was reviewed and approved by the MU Institutional Review Board according to the terms and conditions described below:

<table>
<thead>
<tr>
<th>IRB Project Number</th>
<th>2090562</th>
</tr>
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<tr>
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<td>March 23, 2022</td>
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<td>Approval Date of this Review</td>
<td>May 02, 2023</td>
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<td>Project Status</td>
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<tr>
<td>Risk Level</td>
<td>Minimal Risk</td>
</tr>
<tr>
<td>HIPAA Category</td>
<td>No HIPAA</td>
</tr>
</tbody>
</table>

Informed Consent & Assent - Consent (Exempt Studies Only): #644034

Approved Documents
- Other Study Documents - Eligibility Questionnaire: #644024
- Other Study Documents - Instruments (i.e. surveys): #644038
- Recruitment Materials - Recruitment Materials: #644033

The principal investigator (PI) is responsible for all aspects and conduct of this study. The PI must comply with the following conditions of the approval:

1. No subjects may be involved in any study procedure prior to the IRB approval date or after the expiration date.
2. All study changes must be IRB approved prior to implementation utilizing the Exempt Amendment Form.
3. Major noncompliance must be reported to the MU IRB on the Event Report within 5 business days of the research team becoming aware of the deviation. Major noncompliance are deviations that caused harm or have the potential to cause harm to research subjects or others, and have or may have affected subject’s rights, safety, and/or welfare. Please refer to the MU IRB Noncompliance policy for additional details.
4. The Annual Exempt Form must be submitted to the IRB for review and approval at least 30 days prior to the project expiration date to keep the study active or to close it.
5. Maintain all research records for a period of seven years from the project completion date.
If you are offering subject payments and would like more information about research participant payments, please view the MU Business Policy and Procedure Manual.

Please view the MU HRPP/IRB policies describing IRB exempt and other requirements.

If you have any questions or concerns, please contact the MU IRB Office at 573-882-3181 or email to muresearchirb@missouri.edu.

Thank you,
MU Institutional Review Board
Appendix C. Study Announcement

Call for Participants:
My name is Linda Anderson. I am a registered nurse, and a PhD student at Sinclair School of Nursing at the University of Missouri. I am seeking participants for the following internet survey study: “Hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorders in older women”

This study is looking at the clinical characteristics, symptom burden, and health-related quality of life in older women with hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorder (hEDS/HSD). This study will involve a one-time internet survey that will ask various questions about your current health status, past health history, and your health-related quality of life. The survey should take approximately 20 minutes to complete.

You may be eligible for this study if you are:
- Female
- Age 40 or older
- Have been diagnosed by any licensed healthcare provider with any of the following:
  - Hypermobile Ehlers-Danlos syndrome (hEDS)
  - Hypermobility spectrum disorder (HSD)
  - Ehlers-Danlos syndrome, hypermobility type (EDS-HT)
  - Ehlers-Danlos syndrome, type III (EDS-III)
  - Hypermobility syndrome
  - Joint hypermobility syndrome (JHS)
  - Benign joint hypermobility syndrome (BJHS)

If you are interested in learning more about this study, or participating in this research, please click this link: 
Begin survey

Alternately, you can paste the following URL into your internet browser:
https://showmeportal.missouri.edu/redcap/surveys/?s=EXCXKX9N8KXJRHL7

If you have any questions about this study, feel free to contact me at:

Linda K. Anderson
University of Missouri Sinclair School of Nursing
11 Hospital Drive
Columbia, MO 65201
Email: lka6cb@umsystem.edu
Appendix D. WHO Approval to Use Figure 1.1

WARNING: This message has originated from an External Source. This may be a phishing expedition that can result in unauthorized access to our IT System. Please use proper judgment and caution when opening attachments, clicking links, or responding to this email.

Dear Ms Anderson

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We thank you for your interest in WHO published materials.

Kind regards,
WHO Permissions team

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12. Headings. Paragraph headings in this Agreement are for reference only.

13. Dispute resolution. Any dispute relating to the interpretation or application of this Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the parties or, in the absence of agreement, with the rules of arbitration of the International Chamber of Commerce. The parties shall accept the arbitral award as final.

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225
Appendix E. Permission to use the MDHAQ

<table>
<thead>
<tr>
<th>Contact Name</th>
<th>Linda K. Anderson, BSN, RN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address</td>
<td>4115 Duckhorn Way, Columbia, MO 65203</td>
</tr>
<tr>
<td>Phone Number</td>
<td>573-489-6433</td>
</tr>
<tr>
<td>Email Address</td>
<td><a href="mailto:Lka6cb@umsystem.edu">Lka6cb@umsystem.edu</a></td>
</tr>
<tr>
<td>Study Title or Project Description</td>
<td>Hypermobility Ehlers-Danlos syndrome/hypermobility spectrum disorders in older women: A mixed methods study</td>
</tr>
<tr>
<td>Number of Patients Enrolled</td>
<td>Pending: Target 35 for feasibility/pilot; 60 for full study</td>
</tr>
<tr>
<td>Mode of Administration (Paper, Electronic, Web)</td>
<td>Electronic (REDcap)</td>
</tr>
<tr>
<td>Study Start/End Dates (or Duration of the Project)</td>
<td>dates Summer 2022 for feasibility study, late-2022 to early-2023 for full study</td>
</tr>
<tr>
<td>Translations Needed</td>
<td>None</td>
</tr>
<tr>
<td>License Fee</td>
<td>Waived for non-commercial use</td>
</tr>
</tbody>
</table>
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+1 800-727 5000
www.rws.com
RWS
Life Sciences

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12. Separate license agreement
This license agreement is in force for the use specified on page one of this agreement only. The use of the MDHAQ by the User for any other purpose will require a separate license agreement.

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LICENSOR
By: RWS Life Sciences
Name: Amanda Rosett
Title: Licensing Solutions Lead
Signature: Amanda Rosett
Date:

LICENSEE
By: Linda K. Anderson
Name: Linda K. Anderson
Title: PhD Student
Signature: [Signature]
Date: 3/7/2022
Appendix F. Permission to use the CHIEF-SF

Thank you for your interest in the CHIEF. Feel free to use the instrument in your research and best of luck!

Dave

---

Dave Mellick, PhD  
Director Of Research Operations  
Co-Project Director, Rocky Mountain Regional Brain Injury System  
Co-Project Director TBI Model Systems National Data and Statistical Center  
Tel: 303.789.8563

---

From: Anderson, Linda (MU-Student) <ika6cb@mail.missouri.edu>  
Sent: Saturday, July 9, 2022 2:10 PM  
To: Mellick, Dave <dmellick@craighospital.org>  
Subject: Permission to use the CHIEF-SF

**EXTERNAL EMAIL:** Do NOT click any links or open any attachments unless you trust the sender and are confident the content is safe. For security related questions, please forward the email to InformationSecurity@craighospital.org.

I am a doctoral student at the University of Missouri Sinclair School of Nursing, beginning doctoral research on hypermibile Ehlers-Danlos Syndrome/hypermobility spectrum disorders in older women. I am asking permission to use the Craig Hospital Inventory of Environmental Factors – Short Form (CHIEF-SF) in my research.

My advisor, Kari R. Lane, Ph.D., Associate Professor at Sinclair School of Nursing supervises this study.

I want to use this instrument in the quantitative phase of an online mixed-methods study.

In addition to using the CHIEF-SF, I request permission to reproduce it in my dissertation appendix.

I want to use and reproduce the CHIEF-SF under the following conditions:

- I will only use the CHIEF-SF for my research studies and will not sell or use the instrument for any other purpose.
- I will include a statement of attribution and copyright on all copies of the instrument. Please let me know if you have a preferred attribution statement.
- I will be happy to forward a copy of my completed research study and provide any hyperlinks to published articles if you request.

Please let me know if these terms are acceptable by replying to this email at Ika6cb@umsystem.edu.

Regards,

Linda K. Anderson, BSN, RN  
PhD Student  
Sinclair School of Nursing  
University of Missouri  
573-489-6433 (cell)  
Ika6cb@umsystem.edu
Appendix G. Terms and Conditions for use of RAND SF-36

Terms and Conditions for Using the 36-Item Short Form Survey (SF-36)

RAND hereby grants permission to use RAND 36-Item Short Form Health Survey in accordance with the following conditions, which shall be assumed by all to have been agreed to as a consequence of accepting and using this document:

1. Changes to the Health Survey may be made without the written permission of RAND. However, all such changes shall be clearly identified as having been made by the recipient.

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Appendix H. Survey Instrument

Eligibility Screening

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<thead>
<tr>
<th>Question</th>
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<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am female.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am 40 years old or older.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A licensed healthcare provider has diagnosed me with one of the following:</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hypermobile Ehlers-Danlos syndrome (hEDS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypermobility spectrum disorder (HSD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ehlers-Danlos syndrome, type III (EDS-III)</td>
<td></td>
<td></td>
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<tr>
<td>Ehlers-Danlos syndrome, hypermobility type (EDS-HT)</td>
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</tr>
<tr>
<td>Ehlers-Danlos syndrome, type not specified (EDS)</td>
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</tr>
<tr>
<td>Hypermobility syndrome, Joint hypermobility syndrome (JHS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign Joint hypermobility syndrome (BJHS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am able to read and understand English.</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>I have internet access and can participate in an anonymous online survey that will take approximately 20 minutes.</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Hypermobile Ehlers-Danlos Syndrome/Hypermobility Spectrum Disorder in Older Women

Consent to Participate in the Study

Project Title: Hypermobile Ehlers-Danlos Syndrome/Hypermobility Spectrum Disorders in Older Women

Principal Investigator: Linda K. Anderson, BSN, RN  IRB Assigned Project Number: 2090562

Key Information About the Study

You are invited to participate in a research study. The purpose of this research study is to better understand hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders (hEDS/HSD) in women age 40 and older. You are being asked to complete a one-time, anonymous online survey about your health history, symptoms, and quality of life. This study will have no obvious medical risks to you. Some of the survey questions may make you uncomfortable. You may choose not to answer any question that makes you uncomfortable.

Please read this form carefully and take your time. Let us know if you have any questions before participating. The research team can explain words or information that you do not understand. Research is voluntary, and you can choose not to participate. If you do not want to participate or decide to start then stop later, there will be no penalty or loss of benefits to which you are otherwise entitled.
Purpose of the Research  You are being asked to participate in this study because you have indicated you meet the following criteria:

• Female
• Age 40 or older
• Have been diagnosed by any licensed healthcare provider with any of the following:
  o Hypermobility Ehlers-Danlos syndrome (hEDS)
  o Hypermobility spectrum disorder (HSD)
  o Ehlers-Danlos syndrome, hypermobility type (EDS-HT)
  o Ehlers-Danlos syndrome, type III (EDS-III)  o Ehlers-Danlos syndrome, type not specified
  o Hypermobility syndrome
  o Joint hypermobility syndrome (JHS)
  o Benign joint hypermobility syndrome (BJHS)
• Able to read and understand English
• Have internet access to participate in an anonymous online survey that will take approximately 20 minutes

The purpose of this internet survey is to better understand hypermobile Ehlers-Danlos syndrome and hypermobility spectrum disorders (hEDS/HSD) in women age 40 and older. HEDS/HSD can cause pain, fatigue, and problems with joints in the body. The condition may also be associated with fragile skin, stomach trouble, frequent headaches, and other health problems. Because of these health problems, people with hEDS/HSD can also experience depression, anxiety, and poor health-related quality of life. The condition is poorly understood, and diagnosis delays might be 20 years or more. Right now, we don’t know how hEDS/HSD progresses in women as they get older.

What will happen during the study?

This study will involve a one-time internet survey that will ask various questions about your life. The survey will have questions about your age, where you were born, where you live now, your social life, work, and what medical conditions you have. It will also contain questions about your menstrual and childbearing history and how you feel lately. The survey should take approximately 20 minutes to complete. What are the expected benefits of the study?

Taking part in this survey will not benefit you directly. You may benefit from knowing that you contribute to healthcare researchers’ understanding of hEDS/HSD in older women. We hope this study will improve the diagnosis and treatment of other older women with hEDS/HSD.

What are the possible risks of participating in this study?

There are minimal risks expected when you take part in this study. Some of the survey questions may make you uncomfortable. You may choose not to answer any question that makes you uncomfortable. What other choices do I have if I don’t want to be in this study?

You are not required to be in this study. You may choose not to take the survey, and you may stop the survey at any time. Your decisions about whether or not to take the survey will have no impact on your health care. There will be no penalty or loss of benefits that you might otherwise receive.

Will I receive compensation for taking part in this study?

You will not be compensated for taking part in this study. Will information about me be kept private?

The research team is committed to respecting your privacy and keeping your personal information confidential. We will make every effort to protect your information to the extent allowed by law. When the results of this research are shared, we will remove all identifying information, so the researchers will not know who provided the information.

This survey will include no identifying information, including your name, date of birth, online user name(s), or internet IP addresses. The researchers will have no way to identify you if you participate in the survey.

Who do I contact if I have questions or concerns?

If you have questions about this study or experience a research related injury, you can contact the University of Missouri researcher at:

Linda K. Anderson, BSN, RN
Sinclair School of Nursing
Phone: (573) 489-6433
Email: lka6cb@umsystem.edu
If you have questions about your rights as a research participant, please contact the University of Missouri Institutional Review Board (IRB) at: (573) 882-3181 or email at: muresearchirb@missouri.edu. The IRB is a group of people who review research studies to make sure the rights and welfare of participants are protected.

If you want to talk privately about any concerns or issues related to your participation, you may contact the Research Participant Advocacy at (888) 280-5002 (a free call) or email at muresearchpa@missouri.edu

We appreciate your consideration to participate in this study.

I have read and understood the study information. By clicking YES, I am consenting to participate in this anonymous survey. By clicking NO, I am exiting and closing the survey.

☐ Yes
☐ No

General Information

Thank you for your interest in taking part in this survey.

To get the best information about hypermobile Ehlers-Danlos syndrome/hypermobility spectrum disorder (hEDS/HSD) in older women, it is important for you to answer every question, even if they seem to repeat at times.

Your answers to these questions WILL NOT allow us or anyone else to identify you personally.

This section will ask some general questions about you.

How old are you (in years)?

__________________________

In what year were you born?

__________________________

What was your sex assigned at birth?

☐ Male
☐ Female
☐ Indeterminate or unknown
☐ Prefer not to answer

In what country were you born?

__________________________

In what country do you currently live?

__________________________

How would you describe your racial or ethnic group?

__________________________

How many total years of education have you had?

__________________________

What is your marital status?

☐ Single
☐ Married
☐ Separated
☐ Divorced
☐ Widowed
☐ Prefer not to answer

What best describes your work status?

☐ Employed full-time
☐ Employed part-time
☐ Homemaker
☐ Disabled
☐ Self-employed
☐ Retired
☐ Seeking work
☐ Full-time student
☐ Other
What best describes your current home or living situation?
- Live alone
- Live with spouse or partner or children
- Live with parent(s) or sibling(s)
- Share housing with others (not related)
- Live in a residential care, assisted living, or nursing home facility
- Unhoused
- Prefer not to answer

What best describes your current physical ability?
- Independent or mostly independent
- Mostly housebound
- Housebound
- Bedbound
- Other
- Prefer not to answer

This section will ask general questions about your health history.
What is your current weight? (In pounds)

How tall are you? (In feet and inches)

Feet

Inches

This section will ask you questions about your healthcare providers.
What health professionals do you see on a regular basis - at least once per year? (Select all that apply)
- Primary care provider/general practitioner/family doctor
- Rheumatologist
- Orthopedic physician
- Physiotherapist/physical therapist
- Geneticist
- Psychologist or psychiatrist
- Chiropractor
- Cardiologist
- Neurologist
- Gastroenterologist
- Pain management specialist
- Other
- I see no health professionals on a regular basis (Check all that apply)

If other, please specify:

Do you currently have a primary care provider?
- Yes
- No
If no, what is the reason for not currently having a primary care provider? (select all that apply)

☐ No insurance
☐ Unable to pay for primary care visits or insurance deductible
☐ No primary care provider in the area
☐ Unable to find a primary care provider who is taking new patients
☐ Unable to obtain transportation for primary care visits
☐ The primary care provider left the area or practice. Have not found a replacement
☐ Do not want a primary care provider
☐ Other reason
☐ Prefer not to answer

If other reasons for not having a primary care provider, please specify.

This section will ask you questions about your hypermobility diagnosis.

How old were you (in years) when you first had symptoms of a hypermobility disorder?

[Answer]

Year of symptom onset

[Answer]

How old were you (in years) when the symptoms became severe enough to seek medical diagnosis or treatment?

[Answer]

How old were you (in years) when you were diagnosed with a hypermobility disorder?

[Answer]

Diagnosis year

[Answer]

Time between symptom onset and seeking medical help.

[Answer]

Time between symptom onset and diagnosis:

[Answer]

Time between seeking treatment and diagnosis.

[Answer]

What type of health professional first diagnosed you with a hypermobility disorder?

☐ Primary care provider/general practitioner/family doctor
☐ Rheumatologist
☐ Orthopedic physician
☐ Physiotherapist/physical therapist
☐ Geneticist
☐ Psychologist or psychiatrist
☐ Chiropractor
☐ Cardiologist
☐ Neurologist
☐ Gastroenterologist
☐ Pain management specialist
☐ Other

If other, please specify

[Answer]
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>What was your ORIGINAL diagnosis? (Select one)</td>
<td>○ Hypermobile Ehlers-Danlos syndrome (hEDS)</td>
</tr>
<tr>
<td></td>
<td>○ Ehlers-Danlos syndrome, hypermobility type (EDS-HT)</td>
</tr>
<tr>
<td></td>
<td>○ Ehlers-Danlos syndrome, type III (EDS-III)</td>
</tr>
<tr>
<td></td>
<td>○ Hypermobility spectrum disorder (HSD)</td>
</tr>
<tr>
<td></td>
<td>○ Joint hypermobility syndrome (JHS)</td>
</tr>
<tr>
<td></td>
<td>○ Benign joint hypermobility syndrome (BJHS)</td>
</tr>
<tr>
<td></td>
<td>○ Other type of EDS or connective tissue disorder</td>
</tr>
<tr>
<td></td>
<td>○ None of the above</td>
</tr>
<tr>
<td>If none of the above or other type of EDS or connective tissue disorder</td>
<td><strong>Specify</strong></td>
</tr>
<tr>
<td>Has your diagnosis changed from what it was originally?</td>
<td>○ Yes</td>
</tr>
<tr>
<td></td>
<td>○ No</td>
</tr>
<tr>
<td>What type of health professional provided your most recent diagnosis?</td>
<td>○ Primary care provider/general practitioner/family doctor</td>
</tr>
<tr>
<td></td>
<td>○ Rheumatologist</td>
</tr>
<tr>
<td></td>
<td>○ Orthopedic physician</td>
</tr>
<tr>
<td></td>
<td>○ Physiotherapist/physical therapist</td>
</tr>
<tr>
<td></td>
<td>○ Geneticist</td>
</tr>
<tr>
<td></td>
<td>○ Psychologist or psychiatrist</td>
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<td></td>
<td>○ Chiropractor</td>
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<td></td>
<td>○ Cardiologist</td>
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<tr>
<td></td>
<td>○ Neurologist</td>
</tr>
<tr>
<td></td>
<td>○ Gastroenterologist</td>
</tr>
<tr>
<td></td>
<td>○ Pain management specialist</td>
</tr>
<tr>
<td></td>
<td>○ Other</td>
</tr>
<tr>
<td>If other type of health professional provided your most recent diagnosis</td>
<td><strong>Specify</strong></td>
</tr>
<tr>
<td>If yes, what is your CURRENT diagnosis? (Select one)</td>
<td>○ Hypermobile Ehlers-Danlos syndrome (hEDS)</td>
</tr>
<tr>
<td></td>
<td>○ Ehlers-Danlos syndrome, hypermobility type (EDS-HT)</td>
</tr>
<tr>
<td></td>
<td>○ Ehlers-Danlos syndrome, type III (EDS-III)</td>
</tr>
<tr>
<td></td>
<td>○ Hypermobility spectrum disorder (HSD)</td>
</tr>
<tr>
<td></td>
<td>○ Joint hypermobility syndrome (JHS)</td>
</tr>
<tr>
<td></td>
<td>○ Benign joint hypermobility syndrome (BJHS)</td>
</tr>
<tr>
<td></td>
<td>○ Other type of EDS or connective tissue disorder</td>
</tr>
<tr>
<td></td>
<td>○ None of the above</td>
</tr>
<tr>
<td>If none of the above or other type of EDS or connective tissue disorder</td>
<td><strong>Specify</strong></td>
</tr>
</tbody>
</table>
This section will ask you questions about other medical problems and surgeries.

Do you currently have (or had in the past) any of the following diagnoses? (Select all that apply)
- Fibromyalgia
- Chronic fatigue syndrome/Myalgic encephalomyelitis (CFS/ME)
- Rheumatoid arthritis
- Osteoarthritis
- Osteopenia or osteoporosis
- Irritable bowel syndrome (IBS)
- Endometriosis
- Pelvic organ prolapse
- Gastroesophageal reflux disorder (GERD)
- Temporomandibular joint dysfunction (TMJ)
- Postural orthostatic tachycardia syndrome (POTS)
- Mitral valve prolapse (MVP)
- Obstructive sleep apnea
- Mast cell disorder or mast cell activation syndrome (MCAS)
- Autism/autism spectrum disorder (ASD)
- Anxiety
- Depression
- Self-harm/suicidal thoughts
- Infertility
- Autoimmune disorder
- None of the above

Have you had any of the following surgical procedures (Select all that apply)
- Knee arthroplasty/replacement
- Other knee surgery (not replacement)
- Hip arthroplasty/replacement
- Other hip surgery (not replacement)
- Shoulder arthroplasty/replacement
- Other shoulder surgery (not replacement)
- Other arm or hand surgery
- Other foot or ankle surgery
- Spine surgery
- Pelvic organ prolapse surgery
- Abdominal surgery - laparoscopic
- Abdominal surgery - open (not laparoscopic)

This section will ask about any assistive devices you use (either part-time or full-time)

Manual wheelchair
- No
- Use part of the time
- Use nearly all of the time

Power/electric wheelchair
- No
- Use part of the time
- Use nearly all of the time

Motorized scooter
- No
- Use part of the time
- Use nearly all of the time

Walker
- No
- Use part of the time
- Use nearly all of the time

Cane
- No
- Use part of the time
- Use nearly all of the time

Crutch or crutches
- No
- Use part of the time
- Use nearly all of the time
<table>
<thead>
<tr>
<th>Prosthetic device (e.g., artificial limb)</th>
<th>No</th>
<th>Use part of the time</th>
<th>Use nearly all of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthotic device (e.g. prescription or custom designed brace or splint)</td>
<td>No</td>
<td>Use part of the time</td>
<td>Use nearly all of the time</td>
</tr>
<tr>
<td>Non-prescription or over-the-counter brace - hand, arm, shoulder</td>
<td>No</td>
<td>Use part of the time</td>
<td>Use nearly all of the time</td>
</tr>
<tr>
<td>Non-prescription or over-the-counter brace - foot, ankle, knee, hip, pelvis</td>
<td>No</td>
<td>Use part of the time</td>
<td>Use nearly all of the time</td>
</tr>
<tr>
<td>Non-prescription or over-the-counter brace - neck or back</td>
<td>No</td>
<td>Use part of the time</td>
<td>Use nearly all of the time</td>
</tr>
<tr>
<td>Hearing aid</td>
<td>No</td>
<td>Use part of the time</td>
<td>Use nearly all of the time</td>
</tr>
</tbody>
</table>

**Craig Hospital Inventory of Environmental Factors Short Form (CHIEF-SF)**

Being an active, productive member of society includes participating in such things as working, going to school, taking care of your home, and being involved with family and friends in social, recreational and civic activities in the community. Many factors can help or impair a person's participation in these activities while other factors can act as barriers and limit participation.

First, please tell me how often each of the following has been a barrier to your own participation in the activities that matter to you. Think about the past year, and tell me whether each item on the list below has been a problem daily, weekly, monthly, less than monthly, or never. If the item occurs, then answer the question as to how big a problem the item is with regard to your participation in the activities that matter to you.

(Note: if a question asks specifically about school or work and you neither work nor attend school, check not applicable.)

In the last 12 months, how often has the availability of transportation been a problem for you?  
- Daily  
- Weekly  
- Monthly  
- Less than monthly  
- Never

When this problem occurs has this been a big problem or a little problem?  
- Big problem  
- Little problem
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the past 12 months, how often has the natural environment - temperature, terrain, climate - made it difficult to do what you want or need to do?</td>
<td>Daily, Weekly, Monthly, Less than monthly, Never</td>
</tr>
<tr>
<td>When this problem occurs has it been a big problem or a little problem?</td>
<td>Big problem, Little problem</td>
</tr>
<tr>
<td>In the past 12 months, how often have other aspects of your surroundings - lighting, noise, crowds, etc. - made it difficult to do what you want or need to do?</td>
<td>Daily, Weekly, Monthly, Less than monthly, Never</td>
</tr>
<tr>
<td>When this problem occurs has it been a big problem or a little problem?</td>
<td>Big problem, Little problem</td>
</tr>
<tr>
<td>In the past 12 months, how often has the information you wanted or needed not been available in a format you can use or understand?</td>
<td>Daily, Weekly, Monthly, Less than monthly, Never</td>
</tr>
<tr>
<td>When this problem occurs has it been a big problem or a little problem?</td>
<td>Big problem, Little problem</td>
</tr>
<tr>
<td>In the past 12 months, how often has the availability of health care services and medical care been a problem for you?</td>
<td>Daily, Weekly, Monthly, Less than monthly, Never</td>
</tr>
<tr>
<td>When this problem occurs has it been a big problem or a little problem?</td>
<td>Big problem, Little problem</td>
</tr>
<tr>
<td>In the past 12 months, how often did you need someone else's help in your home and could not get it easily?</td>
<td>Daily, Weekly, Monthly, Less than monthly, Never</td>
</tr>
<tr>
<td>When this problem occurs has it been a big problem or a little problem?</td>
<td>Big problem, Little problem</td>
</tr>
<tr>
<td>In the past 12 months, how often did you need someone else's help at school or work and could not get it easily?</td>
<td>Daily, Weekly, Monthly, Less than monthly, Never, Not applicable</td>
</tr>
<tr>
<td>When this problem occurs, has it been a big problem or a little problem?</td>
<td>Big problem, Little problem</td>
</tr>
<tr>
<td>Question</td>
<td>Options</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>In the past 12 months, how often have other people's attitudes toward you been a problem at home?</td>
<td>Daily, Weekly, Monthly, Less than monthly, Never</td>
</tr>
<tr>
<td>When this problem occurs has it been a big problem or a little problem?</td>
<td>Big problem, Little problem</td>
</tr>
<tr>
<td>In the past 12 months, how often have other people's attitudes toward you been a problem at school or work?</td>
<td>Daily, Weekly, Monthly, Less than monthly, Never</td>
</tr>
<tr>
<td>When this problem occurs has it been a big problem or a little problem?</td>
<td>Big problem, Little problem</td>
</tr>
<tr>
<td>In the past 12 months, how often did you experience prejudice or discrimination?</td>
<td>Daily, Weekly, Monthly, Less than monthly, Never</td>
</tr>
<tr>
<td>When this problem occurs has it been a big problem or a little problem?</td>
<td>Big problem, Little problem</td>
</tr>
<tr>
<td>In the past 12 months, how often did the policies and rules of businesses and organizations make problems for you?</td>
<td>Daily, Weekly, Monthly, Less than monthly, Never</td>
</tr>
<tr>
<td>When this problem occurs has it been a big problem or a little problem?</td>
<td>Big problem, Little problem</td>
</tr>
<tr>
<td>In the past 12 months, how often did government programs and policies make it difficult to do what you want or need to do?</td>
<td>Daily, Weekly, Monthly, Less than monthly, Never</td>
</tr>
<tr>
<td>When this problem occurs has it been a big problem or a little problem?</td>
<td>Big problem, Little problem</td>
</tr>
</tbody>
</table>
### This section will ask questions about your menstrual periods.

<table>
<thead>
<tr>
<th>Question</th>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever had a menstrual period?</td>
<td>Yes, No</td>
</tr>
<tr>
<td>At what age did you have your first menstrual period?</td>
<td></td>
</tr>
<tr>
<td>Did puberty (around the time you started your first menstrual period) impact your hEDS/HSD symptoms?</td>
<td>Symptoms began, Symptoms got worse, Symptoms got better, No change in symptoms, I don't remember</td>
</tr>
<tr>
<td>Have you undergone menopause? (more than one year since last menstrual period)</td>
<td>Yes, No</td>
</tr>
<tr>
<td>How old were you (in years) when you had your last menstrual period?</td>
<td></td>
</tr>
<tr>
<td>How did menopause occur?</td>
<td>Menstrual periods stopped naturally, Ovaries or uterus were surgically removed, Result of chemotherapy or radiation therapy, Not sure, Prefer not to answer</td>
</tr>
<tr>
<td>Did menopause (after menstrual periods stopped completely) impact your hEDS/HSD symptoms?</td>
<td>Symptoms began, Symptoms got worse, Symptoms got better, No change in symptoms, I don't remember</td>
</tr>
</tbody>
</table>

### This section will ask you about your use of hormonal birth control and supplements.

<table>
<thead>
<tr>
<th>Question</th>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you ever used hormonal-based birth control such as birth control pills/patch/ring, or intrauterine device?</td>
<td>Yes, No</td>
</tr>
<tr>
<td>Are you currently using hormonal-based birth control such as birth control pills/patch/ring, or intrauterine device?</td>
<td>Yes, No</td>
</tr>
<tr>
<td>Did the use of hormonal birth control impact your symptoms?</td>
<td>Symptoms began, Symptoms got worse, Symptoms got better, No change in symptoms, I don't remember</td>
</tr>
<tr>
<td>Have you ever taken hormone replacement therapy? (HRT)</td>
<td>Yes, No, Unknown</td>
</tr>
<tr>
<td>Are you currently taking hormone replacement therapy? (HRT)</td>
<td>Yes, No, Unknown</td>
</tr>
<tr>
<td>Did the use of hormone replacement therapy (HRT) impact your symptoms?</td>
<td>Symptoms began, Symptoms got worse, Symptoms got better, No change in symptoms, I don't remember</td>
</tr>
</tbody>
</table>
**This section will ask you about your pregnancy and childbearing history.**

**Have you ever been pregnant?**
- Yes
- No

**[Optional] Are you currently pregnant?**
- No
- Yes

**Did pregnancy impact your hEDS/HSD symptoms?**
- Symptoms began
- Symptoms got worse
- Symptoms got better
- No change in symptoms
- I had more than one pregnancy, and symptoms differed between pregnancies
- I don’t remember

**How many pregnancies have you had? (including live births, still births, miscarriages, abortions, tubal and ectopic pregnancies)**

**How many pregnancies have you carried to 24 weeks or later?**

**How many live births have you had?**

**Have you ever had any of the following pregnancy or childbirth complications? (Select all that apply)**
- Hemorrhage, excessive bleeding before delivery
- Hemorrhage, excessive bleeding during or after delivery
- High blood pressure
- Pre-eclampsia
- 3rd or 4th degree laceration
- Shoulder dystocia
- Fetal injury
- Miscarriage
- Still birth
- Infant death
- Gestational diabetes
- Post-partum depression
- Pre-term labor
- Ectopic pregnancy
- None of the above
- Other complication

**If other pregnancy complication, please specify:**

---

**This section will ask you about your gynecological history.**

**Have you ever experienced any of the following gynecological or women’s health conditions? (Select all that apply)**

**Painful menstrual periods**
- Never
- Had in the past, not currently
- Currently have

**Painful sexual intercourse**
- Never
- Had in the past, not currently
- Currently have

**Endometriosis**
- Never
- Had in the past, not currently
- Currently have

**Infertility**
- Never
- Had in the past, not currently
- Currently have
Vaginal dryness  
- Never  
- Had in the past, not currently  
- Currently have  

Urinary frequency (frequent need to urinate)  
- Never  
- Had in the past, not currently  
- Currently have  

Urinary incontinence (unable to control urination)  
- Never  
- Had in the past, not currently  
- Currently have  

Fecal incontinence (unable to control bowel movements)  
- Never  
- Had in the past, not currently  
- Currently have  

Abnormal Pap smear  
- Never  
- Had in the past, not currently  
- Currently have  

Multi-Dimensional Health Assessment Questionnaire (MDHAQ)

This questionnaire includes information not available from blood tests, X-rays, or any source other than you. Please try to answer each question, even if you do not think it is related to you at this time. Try to complete as much as you can yourself, but if you need help, please ask. There are no right or wrong answers. Please answer exactly as you think or feel. Thank you.

1. Please check (✓) the ONE best answer for your abilities at this time: OVER THE PAST WEEK, were you able to:

1.a. Dress yourself, including tying shoelaces and doing buttons?  
- Without ANY Difficulty  
- With SOME Difficulty  
- With MUCH Difficulty  
- UNABLE To Do  

1.b. Get in and out of bed?  
- Without ANY Difficulty  
- With SOME Difficulty  
- With MUCH Difficulty  
- UNABLE To Do  

1.c. Lift a full cup or glass to your mouth?  
- Without ANY Difficulty  
- With SOME Difficulty  
- With MUCH Difficulty  
- UNABLE To Do  

1.d. Walk outdoors on flat ground?  
- Without ANY Difficulty  
- With SOME Difficulty  
- With MUCH Difficulty  
- UNABLE To Do  

1.e. Wash and dry your entire body?  
- Without ANY Difficulty  
- With SOME Difficulty  
- With MUCH Difficulty  
- UNABLE To Do  

1.f. Bend down to pick up clothing from the floor?  
- Without ANY Difficulty  
- With SOME Difficulty  
- With MUCH Difficulty  
- UNABLE To Do
1.g. Turn regular faucets on and off?  
- Without ANY Difficulty  
- With SOME Difficulty  
- With MUCH Difficulty  
- UNABLE To Do

1.h. Get in and out of a car, bus, train, or airplane?  
- Without ANY Difficulty  
- With SOME Difficulty  
- With MUCH Difficulty  
- UNABLE To Do

1.i. Walk two miles or three kilometers, if you wish?  
- Without ANY Difficulty  
- With SOME Difficulty  
- With MUCH Difficulty  
- UNABLE To Do

1.j. Participate in recreational activities and sports as you would like, if you wish?  
- Without ANY Difficulty  
- With SOME Difficulty  
- With MUCH Difficulty  
- UNABLE To Do

OVER THE PAST WEEK, were you able to:

1.k. Get a good night's sleep?  
- Without ANY difficulty  
- With SOME difficulty  
- With MUCH difficulty  
- UNABLE to do

1.l. Deal with feelings of anxiety or being nervous?  
- Without ANY difficulty  
- With SOME difficulty  
- With MUCH difficulty  
- UNABLE to do

1.m. Deal with feelings of depression or feeling blue?  
- Without ANY difficulty  
- With SOME difficulty  
- With MUCH difficulty  
- UNABLE to do

2. How much pain have you had because of your condition OVER THE PAST WEEK? Please indicate how severe your pain has been.

- 0 NO PAIN  
- 0.5  
- 1.0  
- 1.5  
- 2.0  
- 2.5  
- 3.0  
- 3.5  
- 4.0  
- 4.5  
- 5.0  
- 5.5  
- 6.0  
- 6.5  
- 7.0  
- 7.5  
- 8.0  
- 8.5  
- 9.0  
- 9.5  
- 10 PAIN AS BAD AS IT CAN BE
3. Please check (v) the appropriate spot to indicate the amount of pain you are having today in each of the joint areas listed below:

| 3.a. LEFT FINGERS | ○ None  
|                  | ○ Mild  
|                  | ○ Moderate  
|                  | ○ Severe  |

| 3.b. LEFT WRIST | ○ None  
|                | ○ Mild  
|                | ○ Moderate  
|                | ○ Severe  |

| 3.c. LEFT ELBOW | ○ None  
|                | ○ Mild  
|                | ○ Moderate  
|                | ○ Severe  |

| 3.d. LEFT SHOULDER | ○ None  
|                    | ○ Mild  
|                    | ○ Moderate  
|                    | ○ Severe  |

| 3.e. LEFT HIP | ○ None  
|              | ○ Mild  
|              | ○ Moderate  
|              | ○ Severe  |

| 3.f. LEFT KNEE | ○ None  
|                | ○ Mild  
|                | ○ Moderate  
|                | ○ Severe  |

| 3.g. LEFT ANKLE | ○ None  
|                | ○ Mild  
|                | ○ Moderate  
|                | ○ Severe  |

| 3.h. LEFT TOES | ○ None  
|                | ○ Mild  
|                | ○ Moderate  
|                | ○ Severe  |

| 3.i. RIGHT FINGERS | ○ None  
|                    | ○ Mild  
|                    | ○ Moderate  
|                    | ○ Severe  |

| 3.j. RIGHT WRIST | ○ None  
|                 | ○ Mild  
|                 | ○ Moderate  
|                 | ○ Severe  |

| 3.k. RIGHT ELBOW | ○ None  
|                  | ○ Mild  
|                  | ○ Moderate  
|                  | ○ Severe  |

| 3.l. RIGHT SHOULDER | ○ None  
|                     | ○ Mild  
|                     | ○ Moderate  
|                     | ○ Severe  |

| 3.m. RIGHT HIP | ○ None  
|                | ○ Mild  
|                | ○ Moderate  
|                | ○ Severe  |
3.n. RIGHT KNEE
  - None
  - Mild
  - Moderate
  - Severe

3.o. RIGHT ANKLE
  - None
  - Mild
  - Moderate
  - Severe

3.p. RIGHT TOES
  - None
  - Mild
  - Moderate
  - Severe

3.q. NECK
  - None
  - Mild
  - Moderate
  - Severe

3.r. BACK
  - None
  - Mild
  - Moderate
  - Severe

4. Considering all the ways in which illness and health conditions may affect you at this time, please indicate how you are doing:
  - 0 VERY WELL
  - 0.5
  - 1.0
  - 1.5
  - 2.0
  - 2.5
  - 3.0
  - 3.5
  - 4.0
  - 4.5
  - 5.0
  - 5.5
  - 6.0
  - 6.5
  - 7.0
  - 7.5
  - 8.0
  - 8.5
  - 9.0
  - 9.5
  - 10 VERY POORLY

5. Please check (✓) if you have experienced any of the following over the last month. (Select all that apply.)

- Fever
- Weight gain (> 10 lbs)
- Weight loss (> 10 lbs)
- Feeling sickly
- Headaches
- Unusual fatigue
- Swollen glands
- Loss of appetite
- Skin rash or hives
- Unusual bruising or bleeding
- Other skin problems
6. When you awakened in the morning OVER THE LAST WEEK, did you feel stiff?  

☐ Yes  ☐ No

If yes, please indicate the number of minutes, or hours until you are as limber as you will be for the day.  

_________________________________________________________

Minutes or hours:  ☐ minutes  ☐ hours
7. How do you feel TODAY compared to ONE WEEK AGO? Please check only one.

- Much Better
- Better
- The Same
- Worse
- Much Worse than one week ago

8. How often do you exercise aerobically (sweating, increased heart rate, shortness of breath) for at least one-half hour (30 minutes)? Please check (v) only one.

- 3 or more times a week
- 1-2 times per week
- 1-2 times per month
- Do not exercise regularly
- Cannot exercise due to disability/handicap

9. How much of a problem has UNUSUAL fatigue or tiredness been for you OVER THE PAST WEEK?

- 0 FATIGUE IS NO PROBLEM
- 0.5
- 1.0
- 1.5
- 2.0
- 2.5
- 3.0
- 3.5
- 4.0
- 4.5
- 5.0
- 5.5
- 6.0
- 6.5
- 7.0
- 7.5
- 8.0
- 8.5
- 9.0
- 9.5
- 10 FATIGUE IS A MAJOR PROBLEM

10. Over the last 6 months have you had: [Please check]

<table>
<thead>
<tr>
<th>Event</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>An operation or new illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical emergency or stay overnight in hospital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A fall, broken bone, or other accident or trauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>An important new symptom or medical problem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effect(s) or any medication or drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoke cigarettes regularly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change(s) of arthritis or other medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change(s) of address</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change(s) of marital status</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Change(s) of marital status | ☐ No  
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>
| Change job or work duties, quit work, retired | ☐ No  
|                             | ☐ Yes |
| Change of medical insurance, Medicare, etc | ☐ No  
|                             | ☐ Yes |
| Change of primary care or other doctor | ☐ No  
|                             | ☐ Yes |
| Please explain any "Yes" answer, or indicate any other health matter that affects you. |

**RAND Short-Form 36**

1. In general, would you say your health is:
   - ☐ 1 Excellent
   - ☐ 2 Very good
   - ☐ 3 Good
   - ☐ 4 Fair
   - ☐ 5 Poor

2. Compared to one year ago, how would your rate your health in general now?
   - ☐ 1 Much better now than one year ago
   - ☐ 2 Somewhat better now than one year ago
   - ☐ 3 About the same
   - ☐ 4 Somewhat worse now than one year ago
   - ☐ 5 Much worse now than one year ago

**The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? (Choose one answer for each question.)**

3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports
   - ☐ 1 Yes, limited a lot
   - ☐ 2 Yes, limited a little
   - ☐ 3 No, not limited at all

4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
   - ☐ 1 Yes, limited a lot
   - ☐ 2 Yes, limited a little
   - ☐ 3 No, not limited at all

5. Lifting or carrying groceries
   - ☐ 1 Yes, limited a lot
   - ☐ 2 Yes, limited a little
   - ☐ 3 No, not limited at all

6. Climbing several flights of stairs
   - ☐ 1 Yes, limited a lot
   - ☐ 2 Yes, limited a little
   - ☐ 3 No, not limited at all

7. Climbing one flight of stairs
   - ☐ 1 Yes, limited a lot
   - ☐ 2 Yes, limited a little
   - ☐ 3 No, not limited at all

8. Bending, kneeling, or stooping
   - ☐ 1 Yes, limited a lot
   - ☐ 2 Yes, limited a little
   - ☐ 3 No, not limited at all

9. Walking more than a mile
   - ☐ 1 Yes, limited a lot
   - ☐ 2 Yes, limited a little
   - ☐ 3 No, not limited at all

10. Walking several blocks
    - ☐ 1 Yes, limited a lot
    - ☐ 2 Yes, limited a little
    - ☐ 3 No, not limited at all
11. Walking one block

- 1 Yes, limited a lot
- 2 Yes, limited a little
- 3 No, not limited at all

12. Bathing or dressing yourself

- 1 Yes, limited a lot
- 2 Yes, limited a little
- 3 No, not limited at all

### During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Choose one answer for each question.)

13. Cut down the amount of time you spent on work or other activities

- 1 Yes
- 2 No

14. Accomplished less than you would like

- 1 Yes
- 2 No

15. Were limited in the kind of work or other activities

- 1 Yes
- 2 No

16. Had difficulty performing the work or other activities (for example, it took extra effort)

- 1 Yes
- 2 No

### During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Choose one answer for each question.)

17. Cut down the amount of time you spent on work or other activities

- 1 Yes
- 2 No

18. Accomplished less than you would like

- 1 Yes
- 2 No

19. Didn't do work or other activities as carefully as usual

- 1 Yes
- 2 No

20. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? (Choose ONE answer)

- 1 Not at all
- 2 Slightly
- 3 Moderately
- 4 Quite a bit
- 5 Extremely

21. How much bodily pain have you had during the past 4 weeks? (Choose ONE answer)

- 1 None
- 2 Very mild
- 3 Mild
- 4 Moderate
- 5 Severe
- 6 Very severe

22. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Choose ONE answer.)

- 1 Not at all
- 2 A little bit
- 3 Moderately
- 4 Quite a bit
- 5 Extremely
These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time (during the past FOUR weeks) (Choose ONE answer for each question)

<table>
<thead>
<tr>
<th>23. Did you feel full of pep?</th>
<th>1 All of the time</th>
<th>2 Most of the time</th>
<th>3 A good bit of the time</th>
<th>4 Some of the time</th>
<th>5 A little of the time</th>
<th>6 None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
<td>Options</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 24. Have you been a very nervous person?                                | ○ 1 All of the time  
○ 2 Most of the time  
○ 3 A good bit of the time  
○ 4 Some of the time  
○ 5 A little of the time  
○ 6 None of the time |
| 25. Have you felt so down in the dumps that nothing could cheer you up? | ○ 1 All of the time  
○ 2 Most of the time  
○ 3 A good bit of the time  
○ 4 Some of the time  
○ 5 A little of the time  
○ 6 None of the time |
| 26. Have you felt calm and peaceful?                                    | ○ 1 All of the time  
○ 2 Most of the time  
○ 3 A good bit of the time  
○ 4 Some of the time  
○ 5 A little of the time  
○ 6 None of the time |
| 27. Did you have a lot of energy?                                       | ○ 1 All of the time  
○ 2 Most of the time  
○ 3 A good bit of the time  
○ 4 Some of the time  
○ 5 A little of the time  
○ 6 None of the time |
| 28. Have you felt downhearted and blue?                                 | ○ 1 All of the time  
○ 2 Most of the time  
○ 3 A good bit of the time  
○ 4 Some of the time  
○ 5 A little of the time  
○ 6 None of the time |
| 29. Did you feel worn out?                                              | ○ 1 All of the time  
○ 2 Most of the time  
○ 3 A good bit of the time  
○ 4 Some of the time  
○ 5 A little of the time  
○ 6 None of the time |
| 30. Have you been a happy person?                                       | ○ 1 All of the time  
○ 2 Most of the time  
○ 3 A good bit of the time  
○ 4 Some of the time  
○ 5 A little of the time  
○ 6 None of the time |
| 31. Did you feel tired?                                                 | ○ 1 All of the time  
○ 2 Most of the time  
○ 3 A good bit of the time  
○ 4 Some of the time  
○ 5 A little of the time  
○ 6 None of the time |
| 32. During the past 4 weeks, how much of the time has your physical    | ○ 1 All of the time  
○ 2 Most of the time  
○ 3 Some of the time  
○ 4 A little of the time  
○ 5 None of the time |
|   health or emotional problems interfered with your social activities   | (like visiting with friends, relatives, etc.)?                           |
|   (Choose one number)                                                   |                                                                         |
### How TRUE or FALSE is each of the following statements for you.

(Choose ONE number for each question.)

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>33. I seem to get sick a little easier than other people</td>
<td>□ 1 Definitely true</td>
</tr>
<tr>
<td></td>
<td>□ 2 Mostly true</td>
</tr>
<tr>
<td></td>
<td>□ 3 Don’t know</td>
</tr>
<tr>
<td></td>
<td>□ 4 Mostly false</td>
</tr>
<tr>
<td></td>
<td>□ 5 Definitely false</td>
</tr>
<tr>
<td>34. I am as healthy as anybody I know</td>
<td>□ 1 Definitely true</td>
</tr>
<tr>
<td></td>
<td>□ 2 Mostly true</td>
</tr>
<tr>
<td></td>
<td>□ 3 Don’t know</td>
</tr>
<tr>
<td></td>
<td>□ 4 Mostly false</td>
</tr>
<tr>
<td></td>
<td>□ 5 Definitely false</td>
</tr>
<tr>
<td>35. I expect my health to get worse</td>
<td>□ 1 Definitely true</td>
</tr>
<tr>
<td></td>
<td>□ 2 Mostly true</td>
</tr>
<tr>
<td></td>
<td>□ 3 Don’t know</td>
</tr>
<tr>
<td></td>
<td>□ 4 Mostly false</td>
</tr>
<tr>
<td></td>
<td>□ 5 Definitely false</td>
</tr>
<tr>
<td>36. My health is excellent</td>
<td>□ 1 Definitely true</td>
</tr>
<tr>
<td></td>
<td>□ 2 Mostly true</td>
</tr>
<tr>
<td></td>
<td>□ 3 Don’t know</td>
</tr>
<tr>
<td></td>
<td>□ 4 Mostly false</td>
</tr>
<tr>
<td></td>
<td>□ 5 Definitely false</td>
</tr>
</tbody>
</table>

### Physical and Mental Wellbeing

This section will ask you questions about factors that influence your physical and mental wellbeing. These questions are optional.

As an older woman with hEDS/HSD:

200) [Optional] What types of things improve your physical wellbeing?

_____________________________________________________________________

201) [Optional] What types of things reduce your physical wellbeing?

_____________________________________________________________________

202) [Optional] What types of things improve your mental wellbeing?

_____________________________________________________________________

203) [Optional] What types of things reduce your mental wellbeing?

_____________________________________________________________________
VITA

Linda K. Anderson was born in Fulton, Missouri, to parents whose families hailed from Central Missouri for several generations. She graduated from Sinclair School of Nursing as the first person on both sides of the family to receive a college education. After receiving her Bachelor of Science in Nursing, Linda started her professional career as an intensive care nurse. Over time, she held various professional positions in flight nursing, informatics, quality improvement, and research. Progressive disability from hypermobile Ehlers-Danlos syndrome led her away from hospital nursing and toward chronic illness and disability advocacy, particularly regarding symptomatic hypermobility disorders. Her experiences in the Sinclair School of Nursing Ph.D. program have led to opportunities to collaborate with international researchers about this understudied condition.

Linda is an artist and has displayed and sold her paintings through the Columbia Art League. She lives in Columbia, Missouri, with her husband, Keith, and her daughter Emily.