Systemic Manifestations and Health-Related Quality of Life in Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome-Hypermobility Type

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A thesis submitted in fulfillment of the requirements for the degree of Master of Philosophy at the University of Sydney.

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I, Anne Krahe, hereby declare that the work contained within this thesis is my own and has not been submitted to any other university or institution as part of a whole requirement for any higher degree.

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This is to certify the thesis entitled "Systemic Manifestations and Health-Related Quality of Life in Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome-Hypermobility Type", submitted by Anne Krahe in fulfillment of the requirements for the degree of Master of Philosophy (Medicine), is in a form ready for examination.

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Acknowledgments

I wish to thank my supervisors, Associate Professor Leslie Nicholson and Dr Roger Adams for their support, encouragement, enthusiasm and patience over the course of my studies. With the initial encouragement from Associate Professor Leslie Nicholson, I undertook this course of study and her ongoing interest, diligence, encouragement and guidance has been instrumental in keeping me focused and completing this thesis. Dr Roger Adams has eagerly assisted me throughout the last two years of this course of study and I am very grateful for the wealth of knowledge he provides and his ongoing encouragement and enthusiasm towards this field of research.

I would also like to thank and acknowledge the support provided by Dr Bronwyn Ackermann who assisted in the development of the testing protocol for the physical examination component of the study. Special thanks also goes to Felicia Lim who is a valuable resource of the Discipline of Biomedical Sciences and is always eager to assist and support students in any way she can, she provided me with much needed help and resources on many occasions during my candidature.

I wish to acknowledge all the volunteers who participated in this research, without their eagerness and commitment to furthering the knowledge base in the field of JHS/EDS-HT this thesis would not have been possible.

Lastly I would like to thank my family and friends for the support, encouragement and recognition of my choice to undertaken this course of study and the time commitment it required. The ongoing reassurance and support of my Mum, Dad, Brother and Sister has provided me with the reassurance, support and confidence I required to complete this thesis.

List of Abbreviations:

AQoL-6D	Assessment of Quality of Life – 6 Dimension
BJHS	Benign Joint Hypermobility Syndrome
CFS	Chronic Fatigue Syndrome
CI	Confidence Interval
DASS-21	Depression, Anxiety and Stress Scale – 21 items
EDS	Ehlers-Danlos Syndrome
EDS-HT	Ehlers-Danlos Syndrome Hypermobility Type
FSS	Fatigue Severity Score
HMS	Hypermobility Syndrome
GJH	Generalised Joint Hypermobility
HDCT	Hereditary Disease of the Connective Tissue
HRQoL	Health-Related Quality of Life
JHS	Joint Hypermobility Syndrome
JHS/EDS-HT	Joint Hypermobility Syndrome/ Ehlers-Danlos Syndrome Hypermobility Type
MS	Multiple Sclerosis
PAI	Physical Activity Index
POP	Pelvic Organ Prolapse
POTS	Postural Orthostatic Tachycardia Syndrome
RA	Rheumatoid Arthritis
SD	Standard Deviation
SLE	Systemic Lupus Erythematous
UI	Urinary Incontinence
VAS	Visual Analogue Scale

Abstract

Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome-Hypermobility Type (JHS/EDS-HT) is a hereditary connective tissue disorder associated with both musculoskeletal and systemic manifestations. There is increasing recognition of the significance of the non-musculoskeletal manifestations of the disorder, such as fatigue, orthostatic intolerance, gastrointestinal symptoms and psychological features, the presence of which have challenged the historical view of the condition as a "benign" disorder characterised only by musculoskeletal and cutaneous features. The experience of adults affected by JHS/EDS-HT is often defined by delays in the diagnosis of the condition, dissatisfaction with the diagnostic process and symptom management and the occurrence of a complex array of systemic manifestations associated with the disorder. All of these contribute to a disease morbidity similar to that found in other chronic diseases, significant reduction in overall health-related quality of life (HRQoL) and the progression to functional impairment and disability in some of the adult population affected by the disorder. Over the past three decades, understanding of the disorder has progressed significantly to a point where there is now recognition of the multisystem nature of the condition. There is, however, an ongoing need to further investigate the prevalence, mechanisms and determinants of the systemic manifestations of the condition and the HRQoL experienced by those affected by JHS/EDS-HT.

The primary aim of this thesis is to describe the disease profile of JHS/EDS-HT in an adult population, to provide future direction for the development of targeted management strategies for adults affected by JHS/EDS-HT. Attention will be focused on investigating the prevalence and significance of non-musculoskeletal features of the disorder and their relationship with the overall HRQoL reported by those affected. The prevalence and factors contributing to the severity of fatigue, psychological manifestations of the condition and overall HRQoL, will be a particular focus of this project. Multiple regression analysis will be used to help further define manifestations of the disorder that are predictive of fatigue severity and HRQoL, in order to inform potential future management strategies for the condition.

The aims and objectives of this thesis, a review of the current literature relating to JHS/EDS-HT, and the historical background to the development diagnostic criteria over the past century, are presented in Chapters 1 and 2 of the thesis. To achieve the thesis objectives, two studies were undertaken to investigate the manifestations related to JHS/EDS-HT in an adult population, and specifically to investigate the non-musculoskeletal features of fatigue severity, psychological manifestations of the condition, and overall quality of life experienced by those diagnosed with the JHS/EDS-HT.

The investigation of the prevalence, severity and identification of possible predictors of fatigue severity was undertaken as Study 1 and is found in Chapter 3 of this thesis. This study established that significant fatigue was present in 79.5% of participants and was identified as the most prevalent systemic manifestation of the disorder, with the strongest correlation with overall HRQoL of all reported manifestations. This study successfully identified five manifestations contributing to fatigue severity, including four that are potentially modifiable, accounting for 52.3% of the variance in the severity of the fatigue. The modifiable predictors of fatigue severity identified were; current levels of physical activity participation, satisfaction with the diagnostic and management process experienced by individuals, the frequency of reported orthostatic dizziness, and levels of participation in community and personal relationships, in addition to the self- perceived extent of joint hypermobility identified as a non-modifiable feature. The results of this study provide an important evidence base for future research investigating the potential impact of various management strategies targeting these identified factors contributing to the experience of fatigue in this population.

The systemic nature of JHS/EDS-HT and the multitude of manifestations that are associated with the condition have previously been found to be associated with reduced HRQoL in this population. Study 2, which constitutes Chapter 4 of this thesis, aimed to identify the features of JHS/EDS-HT associated with overall HRQoL and to determine if there are modifiable predictors of HRQoL in this population. This study identified three determinants of HRQoL, including; the number of joints affected by pain, the current level of physical activity participation and levels of depressive symptoms reported by participants, together accounting for 54.9% of the

variance seen in the reported HRQoL of participants. The results of this study provide future direction for interventional studies undertaken with the aim of improving the overall HRQoL experienced by this population by targeting these modifiable determinants.

A summary of the thesis and concluding remarks are presented in Chapter 5. This chapter includes suggestions for future research and clinical interventions in the field of JHS/EDS-HT that have arisen as a result of the 2 included studies.

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Introduction and Literature Review

Background:

Generalised Joint Hypermobility (GJH) is characterised by excessive range of motion of affected synovial joints when referenced against values considered normal for an individual's age, sex and ethnicity (1). Affected individuals often refer to themselves as "double jointed". The hypermobility may be performance enhancing in some sports and performing arts (e.g. gymnastics, high diving, and dance) where it is sometimes seen as a positive selection factor (2). GJH can present as either the extreme of normal joint mobility in the absence of any disorder of the connective tissue or as a feature of a range of disorders where the underlying cause of joint hypermobility is a disorder of the connective tissue.

Joint Hypermobility Syndrome (JHS) and Ehlers-Danlos Syndrome – Hypermobile Type (EDS-HT) are chronic connective tissue disorders in which collagen synthesis is affected. Since connective tissues are found in many of the body's organs, these syndromes are not only characterized by generalised joint hypermobility but a combination of musculoskeletal (e.g. joints, muscles) and multisystem (e.g. skin, gastrointestinal, uro-genital) symptoms and signs. There is a growing consensus that JHS and EDS-HT are indistinguishable conditions and consequently are the same phenotypic disorder (3, 4), referred to as JHS/EDS-HT.

With the progression of research and knowledge relating to JHS/EDS-HT the understanding of the condition has evolved from that of a benign process isolated to the musculoskeletal system to a systemic condition with the potential to significantly reduce the overall quality of life (5) and contribute to substantial disease morbidity (6, 7). As advancements in research have occurred, the significance of the systemic features of JHS/EDS-HT, such as severe fatigue (8), have been noted to be among the most incapacitating of all manifestations associated with the disorder (9). With greater appreciation of the systemic manifestations of JHS/EDS-HT it has been recognized that future specific research is required to further delineate the mechanism, role and impact non-musculoskeletal symptoms have in JHS/EDS-HT.

Generalised Joint Hypermobility:

Identification of Generalised Joint Hypermobility:

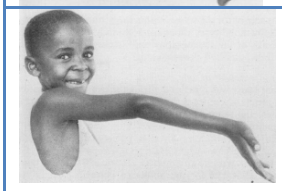
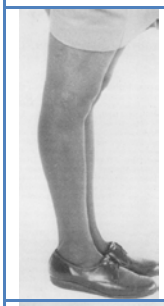
The accurate identification of GJH forms the basis of the diagnosis of JHS/EDS-HT, therefore consideration of what constitutes GJH is imperative to thoroughly appreciate the disorder. Despite the identification of GJH as being a significant element of the diagnostic process for JHS/EDS-HT and a range of other connective tissue disorders, there continues to be a lack of international consensus in establishing a definition that adequately describes the presence of excessive synovial joint mobility while accounting for sex, age and racial differences observed in normal mobility(10). The process of identifying GJH is further complicated by the historical use of a range of tools attempting to identify and quantify the presence of GJH (Table 1.1).

Table 1.1 Commonly used clinical tools to detect GJH

Tool	Assessment Protocol	Method of quantifying GJH	Cut-off score for GJH and variations
Carter Wilkinson Test (1, 11)	1.Passive apposition of the **thumb** to flexor aspect of forearm 2.Passive hyperextension of **fingers** so parallel to forearm 3.Passive hyperextension of the **elbow** >10degrees 4.Passive hyperextension of the **knee** >10degrees 5.Excessive passive Dorsiflexion of the **ankle** and eversion of the foot	1 point assigned to each positive result = /5	• > 3/5 positive tests in both upper limb and lower limb(11) • >3/5 positive results in pairs(1)
Beighton and Horan Test (12)	1.Passive apposition of the **thumb** to flexor aspect of forearm 2. Passive hyperextension of the **elbow** >10degrees 3 Passive hyperextension of the **knee** >10degrees 4. Passive Dorsiflexion of the **little finger** past 90degrees 5. Forward flexion of the **trunk**, with knees extended, so the palms rest easily on the floor	1 point assigned to each positive result present bilaterally Range 0-5	No cut-off for GJH described in initial literature(12)
Rotes Querol et al (13)	1. Passive apposition of the **thumb** to flexor aspect of forearm >185 degrees 2. 2. Passive hyperextension of the **elbow** >10degrees 3 Passive hyperextension of the **knee** >5degrees 4. Passive dorsiflexion of the 2nd finger so the angle of between the table and distal phalanx is >100degrees 5. Forward flexion of the **trunk**, with knees extended, so the palms rest easily on the floor 6. **Shoulder** external rotation > 90 degrees 7. **Cervical** spine rotation >90degrees and side flexion greater than 50degrees 8. Bilateral **hip** abduction >90degrees 9. Dorsiflexion of the **metatarsal-phalangeal** joint >90degrees 10. Lateral flexion of the **lumbar** spine with head and column below horizontal plane	Score range 0-10	Grade severity of GJH: • Grade 1: 0-2 • Grade 2: 3-5 • Grade 3: 6-7 • Grade 4: 8-10
Beighton Score (14)	1.Passive apposition of the **thumb** to flexor aspect of forearm 2. Passive hyperextension of the **elbow** >10degrees 3 Passive hyperextension of the **knee** >10degrees 4. Passive Dorsiflexion of the **little finger** past 90degrees 5. Forward flexion of the **trunk**, with knees extended, so the palms rest easily on the floor	1 point assigned to each positive result Score range 0-9	• Initial description – no cut-off score identified(14) • ≥ 5/9(15) • ≥ 4/9(16)
Hakim-5(17)	1. Can you now (or could you ever) place your hands flat on the floor without bending your knees? 2. Can you now (or could you ever) bend your thumb to touch your forearm? 3. As a child did you amuse your friends by contorting your body into strange shapes or could you do the splits? 4. As a child or teenager did your shoulder or knee cap dislocate on more than one occasion? 5. Do you consider yourself double-jointed?	Score range from 0 – 5 with one point allocated for each positive answer. The Hakim 5 is a Self-assessment tool.	• Cut-off of 2/5 positive responses accurately identifies GJH in 84% of cases.

The Beighton screening tool is the one most commonly utilised tool in both clinical practice and research to identify the presence of GJH (Table 1.2). The protocol for assessing the Beighton score allocates a point for each of 4 specific joints bilaterally and for forward flexion of the trunk, where any exceed a defined range of motion, with a minimum score of 0 and maximum score of 9 possible. The protocol is somewhat ambiguous and studies employing it rarely describe in detailed steps measures taken to standardise each of the five measures (table of the Beighton procedure). The Beighton Score does however have validity assessing GJH in school-aged children when range of motion is objectively measured using goniometry (18, 19), and has a good to excellent inter-rater (19, 20) and intra-rater reliability (20).

Table 1.2 Initial description of the Beighton Scoring system (14)

	Initial description of Beighton Score
	Passive dorsiflexion of the little finger beyond 90degrees *Potential problems with interpretation:* *It is not clear whether the 90 degrees is a composite measure at the MCP, PIP and DIP or just at the MCP*
	Passive apposition of the thumb to the flexor aspect of the forearm *Potential problems with interpretation:* *Is apposition of the tip of the thumb sufficient of should the entire thumb oppose the forearm?*
	Hyperextension of the elbows beyond 10 degrees *Potential problems with interpretation:* *Is visual estimation accurate at angles close to 10 degrees?*
	Hyperextension of the knees beyond 10 degrees *Potential problems with interpretation:* *Is visual estimation accurate at angles close to 10 degrees?*
	Forward flexion of the trunk, with knees straight, so that the palms of the hands rested easily on the floor. *Potential problems with interpretation:* *How far can the hands be placed in front of the feet?*

Prevalence of Generalised Joint Hypermobility

Epidemiological studies investigating the prevalence of GJH in the general population have identified a number of factors, such as age, sex and race, that can influence the extent of joint hypermobility present in otherwise healthy joints. The prevalence of GJH in the paediatric population has been documented to range from 19.2% – 64.6% (21, 22), while the prevalence in the adult population is estimated to range from 4% - 29.8% (23, 24). With increasing age it is accepted that joint mobility reduces, while females typically present with greater joint mobility than males of the same age and gender and race (Table 1.3).

Inconsistencies in the reported prevalence of GJH even in similar samples may be explained by the use of different screening tools, non-universal cut-off scores and differing application of components of the screening tools to assess GJH. Research utilising the Beighton Score does not have consistency in either the application of the components of the test, with the Beighton lacking standardised procedures to define how components of the test should be performed (18) or in the use of a uniform cut-off score to identify the presence of abnormal joint laxity, with scores used in literature ranging from ≥3/9 to ≥5/9 (25) (Table 1.3). Four or more out of nine has been generally been identified as the cut-off point to identify individuals who possess features consistent with GJH (19).

Table 1.3 Prevalence GJH and clinical tools used to establish GJH:

Study	Number of study Participants and Country undertaken	Age in years	Proportion of males with GJH	Proportion of females with GJH	Total proportion of individuals with GJH	Hypermobility Tool utilised and Cut-off score
Lamari et al 2005**(21)**	1120 Brazil	Range 4-7	60%	68.8%	64.6%	Beighton ≥ 4/9
Clinch et al 2011**(22)**	6022 United Kingdom	Mean 13.8	10.6%	27.5%	19.2%	Beighton ≥ 4/9
Jansson et al 2004**(26)**	1845 Sweden	9	37.6%	47.9%	-	Beighton ≥ 4/9
		12	21%	37.8%	-	
		15	15.5%	53%	-	
Al-Rawi et al 1985**(23)**	1774 Iraq	Range 20-24	25.4%	35.8%	29.8%	Beighton ≥ 4/9
Ishaq et al (2010)**(27)**	1000 Pakistan	Mean 25.6 Range 14-60	6.7%	7.8%	7%	Beighton ≥ 4/9
Didia et at 2002**(28)**	550 Nigeria	Range 17-30	8%	17%	12.91%	Beighton ≥ 5/9
Seow et al 1999**(29)**	306 Singapore (Malay/Indian/Chinese)	Range 15-39	-	-	17%	Beighton ≥ 5/9
Larsson et al 1987**(30)**	660 North America	Range 14-68	-	-	9.7%	Carter and Wilkinson Test ≥ 3/5
Beighton et al 1973**(14)**	502 South Africa	>20yrs of age	6%	20%	15.7%	Nil GJH cut-off specified % indicates ≥3/9 Beighton
Klemp et al 2002**(24)**	792 New Zealand (Caucasian and Maori)	>5yrs of age **Female:** Mean 46.10 (Caucasian) Mean 35.06 (Maori) **Male:** Mean 45.54 (Caucasian) Mean 30.49 (Maori)	2% (Caucasian) 2% (Maori)	6% (Caucasian) 9% (Maori)	4% (Caucasian) 6.2% (Maori)	Beighton ≥ 4/9
Kirk et al 1967 **(1)**	64 British	Range 5 - 57	-	-	25%	Carter and Wilkinson Test ≥ 3/5

The evolution of JHS and EDS-HT as a single clinical entity:

Recognition of the historical evolution of knowledge relating to GJH associated with cutaneous, musculoskeletal and systemic manifestations is crucial in understanding the modern day diagnoses of JHS/EDS-HT.

Early documentation of GJH associated with skin signs:

The clinical presentation of joint hypermobility has been referenced in literature since as early as the 4th Century BC. At this time, Hippocrates recorded his observations of members of the Egyptian Scythian tribe, noting that individuals affected by lax joints displayed functional difficulties when throwing javelins and using bows. He noted tribe members performed cautery at multiple sites including the shoulder, wrists and hips in attempts to stabilise joints affected by laxity. Apart from the joint laxity, Hippocrates made further comment that he observed that male members of this population were also affected by joint swelling which resulted in limitations in their functional roles in the tribe with respect to tasks normally undertaken by women (31).

In the medical literature there was little reference to joint hypermobility until the turn of the 20th Century when, in 1892, Dr Tschernogobow a Russian dermatologist provided a comprehensive account of the clinical presentation of two individuals. He reported the presence of hypermobility of the large joints with lax and fragile skin, that had difficulty holding sutures, and molluscoid pseudo tumours of the knees and elbows (32). A short time later in 1901, Edvard Lauriz Ehlers a Danish dermatologist published a case review supporting this presentation, additionally noting an increased predisposition to bruising, developmental delay in walking and recurrent patella subluxations. In 1908, Dr Henri-Alexandre Danlos a French dermatologist suggested that the previously identified lesions affecting the elbows and knees were potentially vascular and inflammatory responses to trauma (32).

In the late 19th century, some individuals presenting with manifestations consistent with the modern definitions of EDS, performed in travelling shows, providing entertainment by demonstrating their excessive skin and joint laxity (Figure 1.1). As a consequence, there was a perception that people exhibiting these signs were “freaks”, with the entertainment value creating a perception of a benign condition. This

opinion may have affected the initial recognition of other serious, debilitating signs and symptoms, associated with skin and joint laxity, which have later been described as a connective tissue dysplasia with diverse phenotypical presentation.

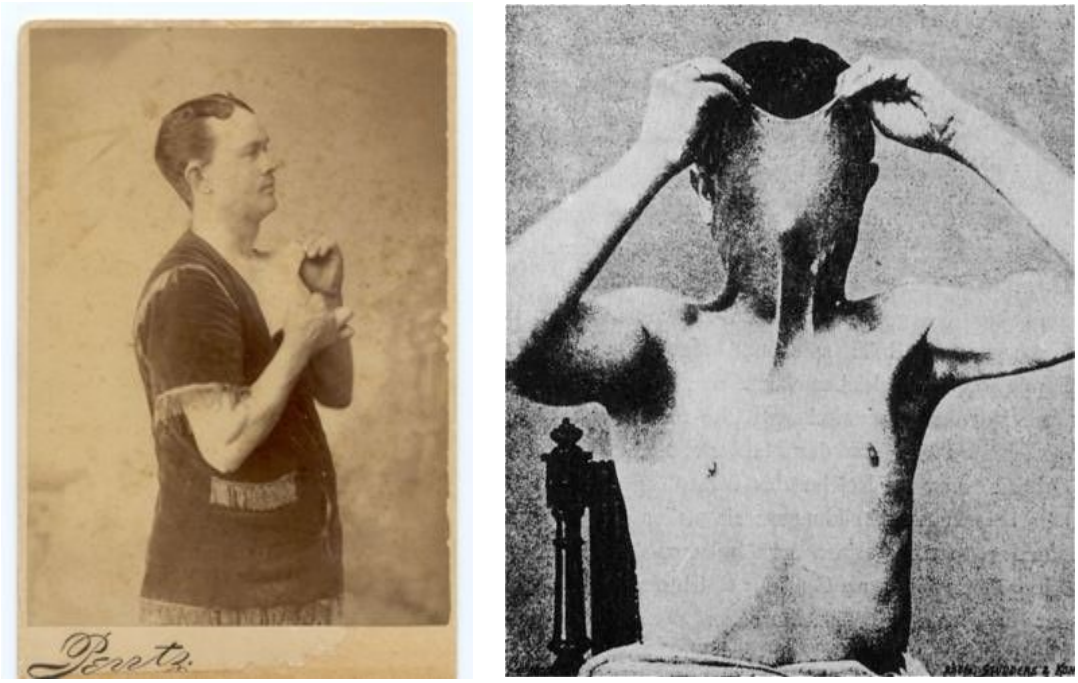


Figure 1.1 Severe skin manifestation in EDS – sufferers portrayed as "freaks" in early travelling shows (Left image (33) and Right image(34)).

Initial identification of a hereditary pattern of expression of GJH:

The documentation in the rheumatology literature of a potential hereditary pattern in the expression of GJH was first made in 1916 when Finkelstein described the clinical presentation of an infant with GJH with a positive familial history of joint laxity(35). He termed this condition Joint Hypotonia and noted that the condition differed from previously documented myotonia, finding no evidence of muscle weakness or reflex changes that were associated with the excessive joint hypermobility (35). The likely familial pattern of inheritance of GJH was again documented in 1927 when Albert Key suggested a potential sex linked trait after investigating a family where the father and all four sons demonstrated joint laxity while female members of the family were apparently unaffected by the condition (36). The author described the condition as limited to hypermobility, in otherwise health joints, without signs of hereditary conditions of the connective tissue. It is worth noting there was reference to the presence of arthralgia in the father and photographic records which demonstrated evidence of papyraceous scarring affecting the skin overlying the anterior knee joints (36), both of which suggest that the joint hypermobility was potentially associated

with both symptomatic joint and cutaneous manifestations. Multiple authors later described the presence of GJH with associated symptomatic joint manifestations. Specific links were drawn between GJH and congenital hip dysplasia (11) in addition to recurrent patella (37, 38) and shoulder dislocations (37).

Divergence in the clinical diagnosis related to symptomatic GJH:

At the turn of the 20th Century, the accounts of research into the clinical presentation of symptomatic hypermobility diverged to form two schools of thought that resulted in the development of two "distinct" conditions. The title given to the clinical presentation by the field of dermatology in 1936 was EDS (39), while over 30 years later in 1967, rheumatologists labelled the condition Hypermobility Syndrome (1). Hypermobility Syndrome has variably been referred to in literature as JHS, BJHS or HMS. The clinical sub-domains of the medical field responsible for developing the initial diagnoses help to explain the differing initial descriptions of the condition. The dermatologic focus on the significance of cutaneous manifestations of EDS rather than joint hypermobility became the basis of the distinction between JHS and EDS in early literature.

Evolution of EDS:

Weber-Parkes first used the diagnostic label of Ehlers-Danlos Syndrome 1936, referring to the condition as a form of congenital developmental mesenchyme dysplasia, otherwise referred to as a Hereditary Disease of the Connective Tissue (HDCT) (39). He described three distinct manifestations of the condition – over-elasticity of the skin, looseness or over-extensibility of joints and friability of the skin and blood vessels (39), with a possible fourth feature relating to altered scar formation which he hypothesised may be a result of the friable nature of the skin. Hypermobility was not seen as pivotal to the diagnosis, instead skin and blood vessel manifestations were clearly noted as the predominant symptoms relating to the condition (39). Jansen later proposed that the phenotype was best explained by a defect of the collagen that comprises connective tissues (40).

The clinical variability observed in EDS prompted the opinion that the diagnosis was likely a HCTD with potentially different genotypes (41). Barabas identified three distinct clinical groups that fell under the umbrella of EDS in 1967. The first was titled the Classical type, presenting with severe joint and skin manifestations but no

varicose veins or arterial ruptures. Varicose type referred to the second subgroup of EDS where individuals were severely affected by varicosities and only demonstrated mild skin and joint involvement. The arterial subtype of EDS affected the third group of individuals, presenting with thin skin, mild skin hyper-extensibility, limited joint hypermobility and an ease of bruising. This subgroup was associated with severe arterial ruptures (41).

In 1986, at the 7th International Congress of Human Genetics, a workshop of geneticists formulated the "Berlin Nosology" of HDCT in an attempt to resolve issues surrounding the nomenclature and classification of connective tissue disorders (42). The Berlin Nosology documented nine subtypes of EDS including EDS-III now referred to as EDS-Hypermobile Type. Although recognising the disorder as an autosomal dominant genetic trait, the description was limited to 3 "cardinal manifestations"; marked articular complications, moderate dermal hyperextensibility and minimal scarring (42).

Following the development of the "Berlin Noslogy" of HDCT the genetic basis of EDS was further investigated culminating in 1997 with a simplified classification system of the disorder, the Villefranche Criteria (15). This new classification system identified 6 subtypes of EDS and provided both Major and Minor criteria to assist in differentiating the subtypes (Table 4). For a diagnosis to be suggested, the presence of at least one major criterion is required while the minor criteria contribute to the diagnosis of the subtype but are insufficient in isolation to form a diagnosis of EDS. EDS-HT remained the only subtype without biochemical or molecular evidence relating to the underlying cause of hypermobility. Generalised Joint Hypermobility, defined as a score of 5/9 or greater arising from using the Beighton scale, and skin hyperextensibility were identified as the major criteria for a diagnosis of EDS-HT (15) (Table 1.4). The diagnosis for EDS-HT remained reliant on clinicians' interpretation of the Villefranche Criteria and subsequent physical examination in the absence of definitive objective tests. The authors of the paper acknowledged the ongoing contention about whether EDS-HT and JHS were distinct entities or whether there are similar phenotypic origins for the disorders (15).

Evolution of JHS:

Initial reference to Hypermobility Syndrome (HMS) reported the condition likely represented the extreme of normal joint mobility rather than a HDCT, representing a benign manifestation of GJH (1). In 1970, Beighton and Horan suggested that the clinical variability in the presentation of GJH and the severity of associated orthopaedic complications and musculoskeletal manifestations were likely to be the result of different genetic traits causing abnormalities in connective tissue (12) as seen in HDCT.

Up until the 1980's HMS was seen as a relatively benign disorder predominately limited to the musculoskeletal system. At this time, Grahame et al (1981) identified a range of non-musculoskeletal manifestations of the disorder including potential Mitral Valve Prolapse, skin thinness and fragile bones. They additionally noted marfanoid habitus without diagnostic features of Marfan Syndrome in their study population presenting with GJH (43). The conclusion of this paper not only referred to the condition as a HDCT but also challenged the perception that HMS was a benign condition isolated to the musculoskeletal system.

Despite increasing evidence that HMS was likely a mild form of a HDCT, the initial Berlin Nosology in 1986 failed to specifically recognise condition as a HDCT. Instead "Familial Articular Hypermobility Syndrome" was documented as a connective tissue disorder with two subtypes – uncomplicated (i.e. GJH without associated orthopaedic manifestations), and the dislocating type. This condition was based on the reports of Beighton and Horan, in 1973, that GJH has two subtypes, one associated with orthopaedic manifestations such as joint dislocations and a second presentation with isolated GJH. At the time of Beighton and Horan's findings there was no definitive statement that the symptomatic version of the condition was a separate condition to HMS (12). This distinction was subsequently made in 1980 when Horton et al suggested that the difference between HMS and Familial Joint Instability Syndrome was the absence of skin manifestations and frequent dislocations in the Familial Joint Instability Syndrome (44).

In response to the increasing references to a multisystem disorder, the British Society for Rheumatology in 1991 proposed a new set of criteria for the diagnosis of HMS.

The criteria contained 2 major and 9 minor criteria, with a diagnosis was only possible if two major criteria or one major and two minor or four minor criteria were present in the absence of a HDCT such as Marfan Syndrome or EDS as defined by the "Berlin Nosology" (45). The inclusion of mitral valve prolapse became controversial when Mishra et al published a study questioning the significance of bone, cardiac, skin and eye abnormalities in JHS. They noted that the prevalence of mitral valve prolapse was not statistically significant compared to individuals unaffected by HMS (46). This study prompted a review of the diagnostic criteria and the subsequent creation of the Brighton criteria with the deletion of mitral valve prolapse as a minor diagnostic criterion (16), labelling the condition Joint Hypermobility Syndrome (Table 1.4).

Table 1.4 Diagnostic criteria for EDS-HT and JHS

Villefranche Criteria for EDS-HT **(15)**	Brighton Criteria for JHS **(16)**
Major Criteria 1. Beighton ≥ 5/9 2. Skin involvement (hyperextensibility and/or smooth, velvety skin) Minor Criteria 1. Recurring joint dislocations 2. Chronic joint or limb pain 3. Positive family history	Major criteria 1. Beighton ≥ 4/9 2. Arthralgia for > 3 months in ≥4 joints Minor criteria: 1. Beighton score 1-3/9 if >50yrs old 2. Arthralgia > 3 months in 1-3 joints or back pain >3 months 3. Dislocation/subluxation in > 1 joint or in one joint on more than one occasion 4. Soft tissue rheumatism ≥ 3 lesions 5. Marfanoid habitus 6. Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring 7. Eye signs: drooping eyelids or myopia or antimongoloid slant 8. Varicose veins or hernia or rectal or uterine prolapse
Diagnosis of EDS-HT suggested when: One or more of the major criteria present. Minor criteria points differentiate between subtypes of EDS but are not sufficient in the absence of major criteria findings for a diagnosis of EDS-HT.	JHS is diagnosed in presence of 1. Two major criteria 2. One major and two minor criteria 3. Four minor criteria 4. Unequivocally affected first degree relative in the absence of Marfan Syndrome or EDS (other than EDS-HT)

Recognition of a single clinical entity – JHS/EDS-HT

In 2009 the first formal acknowledgment occurred that JHS and EDS-HT are phenotypically the same HDCT, following the collaboration of notable Geneticists and Rheumatologists working in the field of HDCT (3). It was observed that although there is significant overlap between the clinical presentation of JHS/EDS-HT and a range of HDCT, including Marfan syndrome, OI type 1 and the other subtypes of EDS, JHS/EDS-HT (Figure 1.2 and Table 1.5) can be identified as a distinct diagnosis.

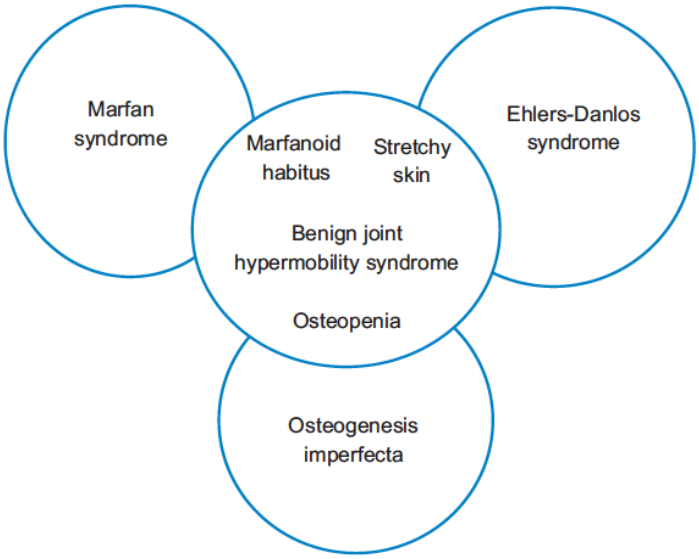


Figure 1.2 Clinical overlap of HDCT(47)

Table 1.5 Clinical features of HDCT(47)

Clinical features	JHS/EDS-HT	Marfan Syndrome	Ehlers-Danlos Syndrome	Osteogenesis Imperfecta
Joint	Hypermobility Arthralgia Dislocations Instability Soft tissue trauma	Hypermobility Arthralgia Dislocations Instability Soft tissue trauma	Hypermobility Arthralgia Dislocation Instability Soft tissue trauma	Hypermobility Arthralgia Dislocation Instability Soft tissue trauma
Skeletal	Marfanoid habitus Osteopenia Slender extremities Pectus deformities Fracture Scoliosis Arachnodactyly Deformity	Marfanoid Habitus Slender extremities Pectus deformities Scoliosis Arachnodactyly	Osteoporosis Fracture Scoliosis Deformity	Osteoporosis Fracture Deformity
Cutaneous	Hyper-extensibility Thinning Striae Atrophicae Papyraceous scars Easy bruising	Hyper-extensibility Thinning Striae Atrophicae Papyraceous Scars Easy Bruising	Hyper-extensibility Thinning Striae Atrophicae Molluscoid Pseudotumours Violaceous papyraceous scars Bruising and Haematoma	Hyper-extensibility Thinning Striae atrophicae Papyraceous scars Easy Bruising
Eyes	Lid Laxity Blue sclera (occasionally)	Ectopia lentis Visual problems		Blue sclera
Vascular	Varicose veins	Aortic dilatation Mitral valve prolapse Aneurysm Subacute bacterial endocarditis	Mitral valve prolapse Intracranial aneurysm Subacute bacterial endocarditis Subarachnoid haemorrhage	Mitral Valve Prolapse Subacute bacterial endocarditis
Muscular laxity	Hernia Rectal/uterine prolapse		Hernia Intestinal/bladder diverticula Rectal/uterine prolapse Neuromyopathy	

Ongoing difficulties establishing single diagnosis:

Despite the consensus that JHS and EDS-HT represent the same distinct clinical entity there are ongoing obstacles to the diagnosis and management of this disorder in clinical practice. To date the condition continues to have two diagnostic criteria (see Table 1.4); the Villefranche criteria for EDS-HT and the Brighton for JHS, being utilised to diagnose each respective condition. As a result, there is use of conflicting Beighton cut-off scores to establish an underlying diagnosis of GJH, with the Brighton requiring a score of at least 4/9 while the Villefranche classification for EDS defines the presence of GJH as a score of $\geq 5/9$.

Unlike other subtypes of EDS, Marfan Syndrome and Osteogenisis Imperfecta the diagnosis of JHS/EDS-HT remains a clinical diagnosis without a confirmed molecular basis for the disorder. This has resulted in the condition remaining a diagnosis of exclusion contributing the extended delays in the diagnosis experienced by many affected by the disorder.

Consistency in the use of diagnostic labels in JHS/EDS-HT continues to be an obstacle to recognising JHS and EDS-HT as a single phenotypic disorder. The condition continues to be inconsistently referred to in literature as JHS/EDS-HT, JHS or EDS-HT without a title that encompasses both conditions under the same diagnostic label. While the impact and potential morbidly of the disorder is likely underplayed in literature with the condition continuing to be referred to as "Benign Joint Hypermobility Syndrome" in some published literature. The delay in developing a single label and diagnostic criteria for the disorder is likely contributing to the delay in referring to both conditions in literature as a single entity and to the ongoing confusion seen in clinical practice surrounding the diagnosis and recognition of JHS/EDS-HT as a multisystem disorder of the connective tissue.

Epidemiology of JHS/EDS-HT:

The true prevalence of JHS/EDS-HT in the general adult population is yet to be fully established. Estimates of the overall occurrence of the condition in Caucasian populations have indicated that the prevalence likely ranges from 0.75% to 2% (48). While documented prevalence of JHS in paediatric populations, identified using the

Brighton Criteria have been reported to range between 4.8% to 17.6% (49, 50). Variations in the prevalence rate is likely to relate to racial and age differences that have previously been identified as contributing to the variation in the expression of GJH in different population and age groups. There is considerably more data referencing the populations presenting with symptomatic GJH without a specific diagnosis compared to research focusing on study populations with a clear diagnosis of JHS/EDS-HT in the adult and paediatric populations affected by this disorder. Symptomatic GJH has been reported to have a prevalence rate of 0.3% in a New Zealand study population ≥ 5 years of age (both Maori and Caucasian ethnicities) (24). While GJH associated with musculoskeletal symptoms in Greek and Indian paediatric samples has been documented to range from 1.7% to 15.4% (51, 52).

Despite the lack of prevalence data relating to JHS/EDS-HT in the adult population, the condition has been identified in up to 33% of patients seeking medical care for gastrointestinal complaints (53) while JHS has been identified in 45% of new referrals to rheumatology clinics (54). The over-representation of JHS/EDS-HT patients in both rheumatology and gastroenterology clinics highlights the potential for significant morbidity associated with the disorder.

Clinical characteristics of JHS/EDS-HT

The clinical presentation of JHS/EDS-HT is variable, the features of the condition that form the basis of the diagnosis focus on the presence of arthralgia, musculoskeletal and cutaneous manifestations of the disorder. In addition to these features, individuals affected by the disorder can present with a range of systemic manifestations including but not limited to urogenital, gastrointestinal, cardiovascular, neurological and psychological features (9) (Figure 1.3). The presence and combination of pain, musculoskeletal, cutaneous and systemic features, described below, contribute to disease morbidity (7) with associated reduction in participation in activities of daily living, low levels of physical activity, significantly impaired overall quality of life (5) and resultant disability (6).

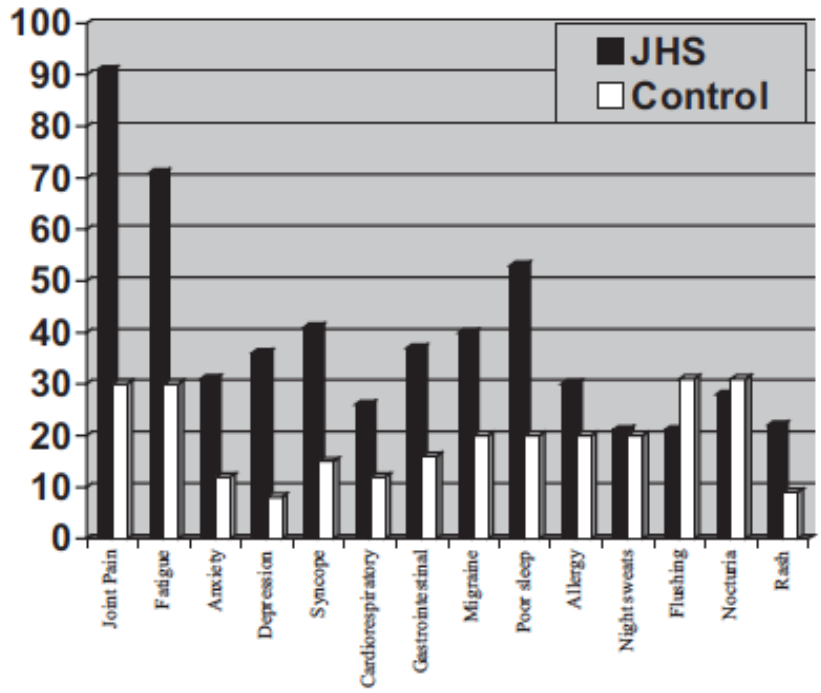


Figure 1.3 Frequency of reported manifestations of JHS (55)

Musculoskeletal manifestations of JHS/EDS-HT:

Musculoskeletal (MSK) manifestations of JHS/EDS-HT underpin the diagnostic criteria for both JHS (16) and EDS-HT (15). Historically MSK and cutaneous features were identified as the predominant manifestations of JHS/EDS-HT with little recognition of the systemic co-morbidities associated with the condition (56). MSK symptoms such as joint hypermobility, joint pain and recurrent dislocations have been reported to occur in up to 79% of individuals prior to 18 years of age, while 99% of individuals with a diagnosis of JHS/EDS-HT report symptoms that relate to the MSK system (9). Development motor delays have been reported in the paediatric populations affected by JHS/EDS-HT with 21.4% found to have motor delay or clumsiness (57), reduced coordination paediatric (36%) (58) and delay in the onset of walking of greater than 15 months (58). Symptoms relating to the MSK system are typically the manifestation of the disorder that prompts an individual to seek professional advice and management for their hypermobility with JHS/EDS-HT accounting for over 45% of referrals to rheumatology clinics (54). The prevalence and types of MSK manifestations associated with of JHS/EDS-HT can be found in Table 1.6.

Table 1.6 MSK manifestations related to JHS/EDS-HT

MSK Manifestation of JHS/EDS-HT	Prevalence
Hypermobility – Childhood	100% (59)
Residual Hypermobility - Adult	65% (59) 73.8% (57) 97% (60)
Arthralgia / Joint pain	100% (61) 83.3% (57) 95.2% (59) 74% (Paediatric populations) (58)
Joint locking	11.1% (61)
Joint dislocation	96.3% (61) 73.8% (Recurrent Dislocations) (57) 85.7% (59)
Joint swelling	3.7% (61) 38% (paediatric) (58)
Muscular pain	29.6% (61) 85.7% (Recurrent) (57) 76.2% (Recurrent/Chronic) (59)
Tendinitis	25.6% (61)
Soft tissue lesions	42.8% (≥ 3 lesions) (57)
Muscle weakness	14.8% (61) 77% (60)

Pain:

Musculoskeletal pain has long been acknowledged as a significant feature of JHS/EDS-HT, with polyarthralgia (>3 months) constituting a major criterion for the diagnosis of JHS using the Brighton scoring system (16) and chronic joint or limb pain constituting a minor criterion for the diagnosis of EDS-HT using the Villefranche Criteria (15). With progression of knowledge, the prevalent systemic features of JHS/EDS-HT including neuropathic, visceral, headache and dysfunctional pain in addition to pain arising from the musculoskeletal system have been recognised (62) (Figure 1.4).

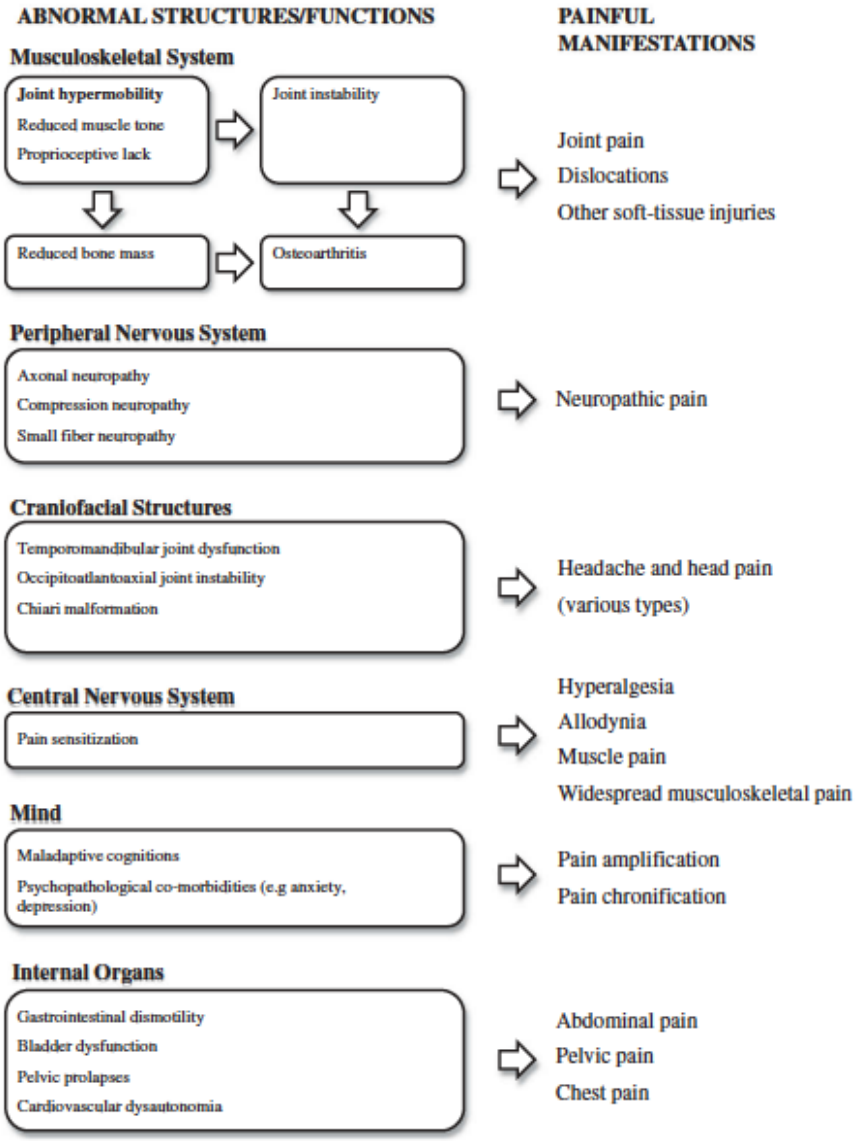


Figure 1.4 Factors contributing to pain in EDS (62)

Pain relating to the musculoskeletal system is a frequently reported manifestation of JHS/EDS-HT with joint pain identified as having the greatest impact on overall quality of life when compared to all other self-reported manifestations of the disorder (9). Chronic pain has been documented to affect up to 100% of individuals with a diagnosis of JHS/EDS-HT (63), while 85.7% report experiencing progressively worsening pain (63). Musculoskeletal pain is typically widespread affecting multiple joints, with a study investigating pain in EDS-HT reporting the mean number of joints affected as 8.9, while the intensity of pain experienced by individuals with a diagnosis of EDS-HT was reported as 5.3/10 on a Visual Analogue Scale (VAS) (63). Similar

results were found in another sample of EDS-HT patients (N=162), with 98% of participants experiencing pain, the mean of which was reported as 49.1/100 with 91% of participants using analgesia. The severity of pain and the number of patients reporting pain ($p \leq 0.001$ for both) was significantly greater for the hypermobile than vascular subtype of EDS (60). The prevalence of pain ($p < 0.001$) and the most severe pain experienced ($p = 0.014$) was also significantly greater in the hypermobile compared to the classical subtype of EDS (60). The mechanisms behind musculoskeletal pain are thought to relate to both acute tissue micro-trauma, caused by repetitive subclinical articular damage related to joint instability, and to soft tissue injuries, joint subluxation and dislocations and the progression to widespread non-specific pain, all of which likely contribute to the development of chronic pain over time (62, 64). Other factors which play a role in the development and maintenance of chronic pain include; kinesiophobia (57) and subsequent deconditioning, significant fatigue, reduced quality of life and functional capacity. Figure 1.5 demonstrates a model hypothesized to explain the pathogenesis of chronic pain in JHS/EDS-HT (65).

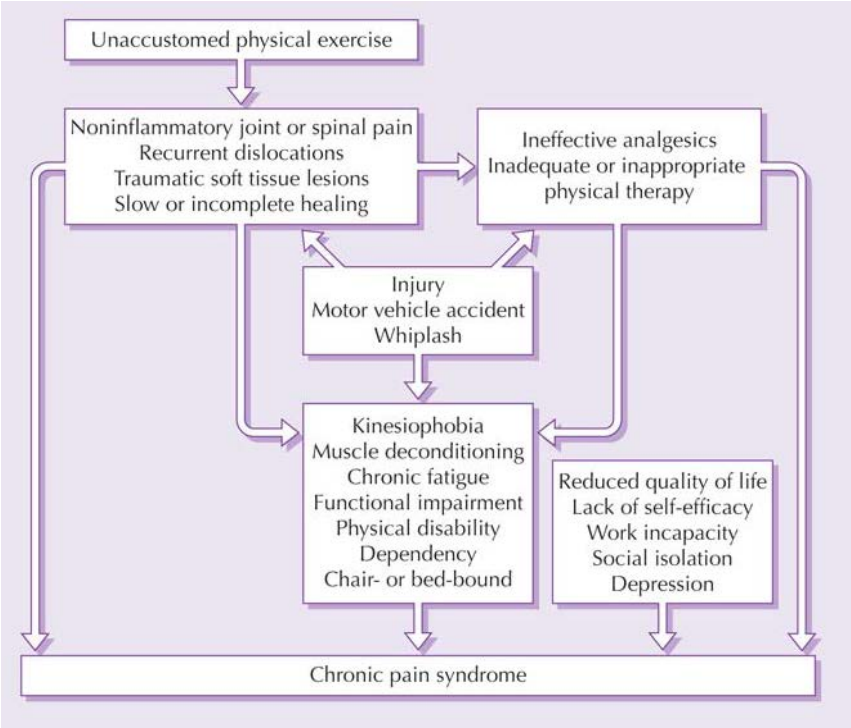


Figure 1.5 Hypothesized pathogenesis of chronic pain (65)

Pain identified as being neuropathic in origin has been reported to affect between 50% (66) and 68% (67) of individuals with JHS/EDS-HT, challenging the historical beliefs that pain experienced in JHS/EDS-HT is predominately musculoskeletal in origin. The underlying mechanisms of neuropathic pain, is thought to relate to axonal and compressional neuropathies related to repeated subluxations and dislocations of joints and nerves (62). Small fibre neuropathy has also been identified in a cohort of EDS subjects, JHS/EDS-HT accounting for 83% of the sample, finding all participants had symptoms of neuropathic pain and associated small fibre neuropathy (68).

Central sensitization, evidenced by the presence of significantly lower pain pressure thresholds in EDS-HT compared to unaffected control subjects has been proposed as a potential mechanism behind the progression to chronic wide-spread pain in EDS-HT (66). Generalised hyperalgesia characterized by widespread reduced pain pressure thresholds in regions unaffected by pain has been linked to chronic pain states such as fibromyalgia and chronic back pain (66). The documentation of this phenomenon in EDS-HT, provides evidence that generalized secondary hyperalgesia may play a role in the development of widespread chronic pain in this population.

Cutaneous manifestations:

Cutaneous manifestations of JHS/EDS-HT are features frequently associated with the condition, with elements well recognized as pivotal signs requiring evaluation when diagnosing either JHS or EDS-HT. Skin manifestations which have been linked to JHS/EDS-HT include striae (stretch marks), typically wide and atrophic, delayed healing associated with the development of atrophic scars (48), skin laxity or hyper-extensibility, skin fragility, easy bruising and piezogenic papules (59) (Figure 1.6).

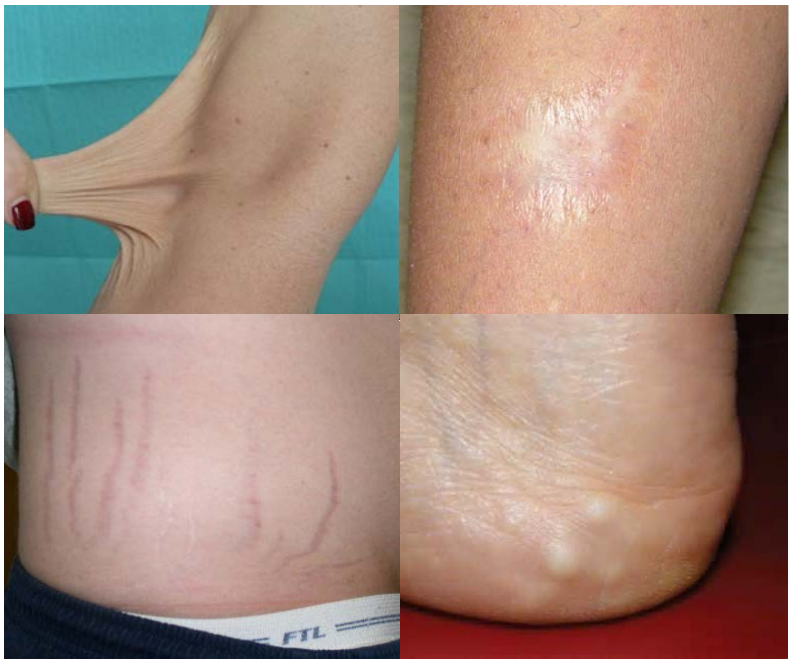


Figure 1.6 Cutaneous manifestations of JHS/EDS-HT:

Top Left – skin hyper-extensibility; Top Right – Papyraceous scaring; Bottom Left – Stria atrophicae; Bottom Right: Piezogenic papules.

The descriptions of cutaneous manifestations of JHS and EDS-HT accentuate the clinical overlap between this condition, other subtypes of EDS and a number of HDCT. Both the Villefranche criteria for EDS-HT, and the Brighton criteria for JHS, reference skin hyper-extensibility. However, discrepancy exists when considering other cutaneous manifestations of JHS and EDS-HT. The Brighton criteria records striae, thin skin and abnormal scarring (15), previously described as atrophic (48), as minor criteria for the diagnosis of JHS. Smooth, velvety skin features as a major criterion together with skin hyper-extensibility for the diagnosis of EDS-HT, however the Villefranche criteria notes the presence of atrophic scars associated with of GJH as suggestive of the classical subtype of EDS not EDS-HT (15).

The clinical evaluation of cutaneous manifestations of JHS/EDS-HT creates additional impediment when attempting to uses these signs objectively in the diagnosis of JHS/EDS-HT, as there is no universal method for assessing these features. Attempts to standardize the testing protocol for these features have the demonstrated potential for inter-rater reliability to be substantial in the assessment of skin extensibility and bruising, and good for scarring (69). However, testing for skin consistency or quality (i.e. thin/velvety or smooth) was only fair when using a standardized testing protocol (69). As a result, the authors suggested excluding skin

consistency from the diagnostic criteria for JHS/EDS-HT and recommend setting an upper limit for normal skin extensibility to 3cm to improve diagnostic accuracy (69).

Systemic Manifestations of JHS/EDS-HT:

Recognition of the types and significance of non-MSK related manifestation of JHS/EDS-HT has increased considerably over the past 3 decades. Non-musculoskeletal manifestations have been reported to affect up to 95% of individuals with JHS/EDS-HT (70). Non-MSK manifestations of JHS/EDS-HT have been reported to affect nearly all body systems and include, cardiovascular, gastrointestinal, psychological, severe fatigue, neurological and genitourinary systems (9). Despite increasing reference in the literature to the systemic symptoms and signs of JHS/EDS-HT challenges continue to exist in the recognition of the condition as a complex systemic condition (56, 71).

Cardiovascular Manifestations:

A range of cardiovascular conditions have been linked to the presence of JHS/EDS-HT including structural, electrophysiological and orthostatic intolerance. Autonomic dysfunction is thought to play a role in symptoms related to orthostatic intolerance. Early literature described catastrophic vascular complications related to EDS including arterial dissections and aneurysms, electrocardiographic abnormalities, congenital abnormalities, and cardiac valve disorders (72). These studies were conducted prior to the development of the Villefranche Criteria and reported on participants with undifferentiated subtypes of EDS. Since the development of the Villefranche and Brighton criteria the prevalence, type and severity of cardiovascular manifestations associated with JHS/EDS-HT have been better defined.

Structural abnormalities associated with the presence of JHS/EDS-HT include tricuspid, mitral and aortic valve disorders and aortic root enlargement (73). There has been contradictory evidence to support an increased rate of mitral valve prolapse (MVP) compared to the general population, with the initial inclusion of the condition in the diagnostic criteria for JHS. MVP was subsequently removed from the revised Brighton Criteria following the finding of no statistical significance between the presence of MVP in a population affected by JHS (10%) compared to a healthy

control sample (7%) (46). Despite the deletion of MVP from the diagnostic criteria for JHS the prevalence of MVP documented in this population continues to vary widely, ranging from 0% (73) to 79% (74) . Potential reasons accounting for the variation in the reported prevalence of MVP in JHS/EDS-HT studies include the use of small sample sizes (<30 participants) (74-76), use of varying criteria to diagnose MVP (46) and changes and improvements in sonographic technology utilized (M-Mode compared to two dimensional echocardiogram) (75). Electrophysiological abnormalities relating to cardiac function at rest have shown significant increase in PR interval and P wave duration in those with EDS-HT compared to healthy control subjects (75).

Orthostatic intolerance is a significant non-musculoskeletal complaint associated with JHS/EDS-HT with a reported prevalence ranging from 74% (77) to 78% (78). Postural Orthostatic Tachycardia Syndrome (POTS) is the most frequently reported form of orthostatic intolerance in this population, its prevalence ranging from 15% (78) to 41% (77). POTS is clinically diagnosed, in the absence of any other chronic debilitating illness, when ongoing symptoms of orthostatic intolerance (Table 1.7), are present for more than 6 months and associated with an increase in heart rate of $\geq$ 30beats/min or a heart rate of > 120 beats per minute within 10mins of assuming an upright posture or undergoing the Head Up Tilt Test (HUTT) (79). In addition to POTS, between 22% (78) and 26% (77) of individuals experience orthostatic intolerance caused by orthostatic hypotension in response to upright postures, which is defined as a sustained reduction in systolic blood pressure of > 20mmHg or >10mmHg of diastolic blood pressure within 3 min of assuming an upright posture or HUTT (79) .

Orthostatic intolerance is linked to a range of symptoms including dizziness, fatigue, orthostatic palpitations, exercise intolerance, headache, reduced concentration, near syncope and syncope (Table 1.7). These symptoms are typically preceded by orthostatic changes and can be exacerbated by physical exertion and heat (80).

Although the exact mechanisms behind orthostatic intolerance in JHS/EDS-HT is yet to be established it is thought to relate a complex interplay between autonomic nervous system dysfunction, connective tissue laxity, deconditioning, depression and

pain induced sympathetic arousal (77). The likely mechanism of dysautonomia associated with EDS-HT related orthostatic intolerance has been supported by evidence of higher resting systolic and diastolic blood pressure and heart rate in individuals with EDS-HT compared to control subjects suggestive of increased sympathetic activity at rest (77). In addition, tests for autonomic reactivity have shown individuals with EDS-HT have reduced sympathetic response to acute challenges to the cardiovascular system (such as the HUTT and valsalva manouvres) (77, 78) with reactions to testing suggestive of insufficient sympathetic vasoconstriction. Neuropathic mechanisms such as impaired peripheral sympathetic nerve function have been supported by findings of decreased sweat response, when testing the quantitative sudomotor axon reflex test, in patients with EDS-HT potentially contributing to orthostatic intolerance (77). The potential influence of connective tissue laxity to orthostatic intolerance has been demonstrated by the association between higher Beighton scores and lower resting blood pressure and higher heart rate on othostatic challenge, suggestive of reduced peripheral vascular resistance contributing to venous pooling during upright positioning (77). Skin laxity has been identified as predictive of sympathetic dysfunction in EDS-HT (77). The suggestion that deconditioning plays a role in orthostatic intolerance in JHS/EDS-HT through changes such as reduced plasma volume and changes to baroreflex buffering and adrenoreceptor sensitivity is yet to be confirmed (77, 78, 81).

Table 1.7 Features of Orthostatic Intolerance in JHS/EDS-HT

Symptom related to Orthostatic Intolerance:	Prevalence of symptoms of Orthostatic Intolerance in JHS/EDS-HT
Dizziness	58% (82) 88% (78)
Fatigue	58% (82) 67% (central) (78) 71% (physical) (78)
Orthostatic Palpitations	54% (82) 90% (78)
Near syncope	58% (82) 83% (78)
Syncope	56% (78) 62% (82)
Headache/migraine	73% (82) 75% (78)
Impaired concentration	71% (78)

The autonomic symptom burden associated with EDS-HT is significantly greater compared to both the classical and vascular subtypes of EDS and comparable to the autonomic symptom burden in observed in fibromyalgia (81). When autonomic symptoms related to JHS are divided into three categories, (pre)syncope, cardiorespiratory and gastrointestinal, the presence of all three symptom categories is associated with a 3 times higher incidence of fatigue compared to individuals not affected by JHS (55). Fatigue has also been linked to a specific diagnosis of POTS, with reports of up to 58% of individuals with JHS-related POTS suffering from clinically significant fatigue (82), while 95% of all individuals diagnosed with POTS report fatigue associated with the disorder (83).

Genitourinary manifestation:

Genitourinary manifestations and obstetric complications have been associated with JHS/EDS-HT (Table 1.8) and may occur at a younger age in this population compared to the general population. The prevalence of urinary incontinence affecting women with the condition has been reported to range from 42.1% (84) to 73.3% (85), while 26% of children diagnosed with JHS have reported frequent urinary incontinence (86). Despite the majority of affected women rating the leakage of urine as small, over half of these women reported that it severely affected their QoL compared to only one third of unaffected women who also experience urinary incontinence (87). In the pediatric population incontinence was also found to be a predictor of poor HRQoL (86).

Table 1.8 Genitourinary manifestations of JHS/EDS-HT:

Genitourinary Manifestation	Study	Sample characteristics	Findings
Incontinence:	Arunkalaivanan et al 2009 (88)	148 adult female individuals with BJHS	• 68.9% reported urinary incontinence (stress or urge incontinence) • 14.9% Fecal incontinence
	Jha, Arunkalaivanan and Situnayake 2007 (87)	30 Female individuals with BJHS Mean age 40yr 30 Control Mean age 36yrs	• 60% urinary incontinence in BJHS compared to 30% experiencing urinary leakage in control • 67% of BJHS with urinary incontinence rated amount of leakage as small • 55% in BJHS compared to 33% of control individuals who experienced incontinence reported severely affected QOL
	Mastoroudes et al 2013a (85)	60 female individuals with BJHS 60 control participants Mean 39.4yrs	• 73.3% of prevalence of urinary incontinence in BJHS group compared to 48.3% • 62% BJHS compared to 38.3% in control reported urge incontinence • 63.3% compared to 36.7% stress incontinence Urinary manifestations with significantly greater frequency compared to control ($p < 0.05$): • Urinary frequency • Nocturia • Nocturnal enuresis • Intercourse related incontinence • Urinary tract infections • Bladder pain • Urge incontinence
	McIntosh et al 1995 (84)	36 female participants with EDS (type I, (II and III) Mean age40.3yrs 19 EDS-III Mean age 38.3yrs	• 52.8% of participants experienced Incontinence • 42.1% of EDS-III reported incontinence, with stress incontinence accounting for 84.6% of incontinence type.
Prolapse:	Mastoroudes et al 2013b (89)	60 Female participants with BJHS 60 Control participants Mean age 39.4	Pelvic organ prolapse (POP): • 73.3% of BJHS participants had a clinically significant POP compared to 35% of control subjects. Vaginal bulge symptoms increase prevalence in BJHS compared to control: • Heaviness or dragging from the vagina or lower abdomen as day goes on

			(28.3%) • Discomfort in vagina (25%) or back (60%)worse when standing and eased by lying • Backache worsen vaginal discomfort (36.7%) POP symptoms in BJHS associated with significantly worse QOL compared to control.
	McIntosh et al 1995 (84)	36 female participants with EDS (type I, (II and III) Mean age40.3yrs 19 EDS-III Mean age 38.3yrs	Prolapse: • 25.9% of all EDS participants • 33.3% of EDS-III participants
Obstetric complicaitons:	Morales-Rosello, Hernandez-Yago and Pope 1997 (90)	Case review – Pregnancy related published cases of 39 EDS-III Females	• 15% preterm delivery/premature rupture of membranes • 10% Gestational intrapartum haemorrhage • 5% post partum haemorrhage • 82% live born
	Lind and Wallenburg 2002 (91)	Retrospective study – 46 women with EDS, 128 pregnancies 43 pregnancies of 33 unaffected women (control) 33% EDS-III	• Pelvic pain and instability 26% in affected individuals compared to control 7% • Preterm delivery 21% compared to 40% unaffected control • Post partum haemorrhage 19% compared to 7% control • Complicated perineal wounds 8% in EDS compared to 0% in control

Obstetric complications relating to antenatal pelvic pain, post-partum hemorrhage and complicated wound healing have been shown to have higher rates of occurrence in women affected by all subtypes of EDS compared to the general community (91). There have also been reports of varicose veins, hernia, antenatal hemorrhage (92) and preterm labour/premature rupture of membranes (90, 92) associated with both EDS-HT and other subtypes of EDS. There are, however, few large studies investigating the prevalence of obstetric complications in JHS/EDS-HT compared to that found in the general community.

The presence of pelvic organ prolapse in JHS/EDS-HT has been reported to vary from 19% (59), in self report questionnaires, to 73.3% of women formally assessed with questionnaires and physical examination (89). This suggests study participants may under report or fail recognize the condition or its symptoms

Gastrointestinal manifestations:

Significant and catastrophic gastrointestinal manifestations associated with EDS have been recognized and recorded in the literature since the mid 1900's with initial reports of gastrointestinal complications relating to EDS focused on rare events such as spontaneous intestinal perforation and significant gastrointestinal hemorrhage (93). In 1969, Beighton, Murdoch and Votteler described structural gastrointestinal abnormalities associated with EDS as occurring more frequently and being associated with less morbidity and mortality. These abnormalities included external hernia (femoral, inguinal and umbilical), eventration of the diaphragm, rectal prolapse and diverticular disease of the colon (93). With the identification of clearer subtypes of EDS using the Villefranche criteria, knowledge relating to the risks associated with catastrophic gastrointestinal complications in JHS/EDS-HT has become better understood. It is now recognized that gastrointestinal perforations and hemorrhage almost exclusively occur in the vascular subtype of EDS, however JHS/EDS-HT has been linked with a range of structural and functional gastrointestinal symptoms associated with disease morbidity and quality of life (53) (Table 1.9). It has been estimated that up to 33% of individuals seeking tertiary care for gastrointestinal symptoms fulfill the Brighton criteria and have undiagnosed JHS (94).

Table 1.9 Frequently reported gastrointestinal symptoms in JHS/EDS-HT

Gastrointestinal manifestations	Prevalence in JHS/EDS-HT(%)
Dysphagia	• Adult 14.3% (95) • Adult 11.1% (96)
Dyspepsia/gastritis	• Adult 14.3% (95) • <10years of age 8% (97) • >40years of age 48% (97) • Adult 10.7% (96)
Postprandial fullness	• Adult 41.4% compared to control 27.1% (94) • Adult 7% (96)
Gastro-oesophageal Reflux Disease (GORD)/Heartburn	• Adult 52.4% (95) • Adult 33% (compared to 23.5% control) (94) • < 10 years of age 57.1% (97) • > 40 years of age 74% (97) • Adult 57.1% (59) • Adult 38% (96)
Bloating	• Adult 57.1% (95) • Adult 17% (96)
Nausea	• Adult 57.1% (95) • Adult 44.3% (96)
Vomiting	• Adult 57.1% (95) • Adult 24.7% (96)
Recurrent Abdominal Pain	• Adult 76.2% (95) • < 10 years of age 26% (97) • > 40 years of age 68% (97) • Adult 61.9% (59) • Adult 56.1% (96)
Abnormal colorectal transit	• Adult 100% (95)
Constipation/diarrhea	• Adult 76.5% (95) • < 10 years of age 54% (97) • > 40 years of age 72% (97) • Adult 33.3% (59) • Adult constipation 42.4% (96)
Abdominal hernia	• <10 years of age 10% (97) • >40 years of age 20% (97) • Adult 4.8% (59)

Structural abnormalities of the gastrointestinal tract, previously linked to JHS/EDS-HT, include hernias (59, 93); hiatus, inguinal, femoral and umbilical, megalocolon (abnormally wide colon) (98), dolichocolon (abnormally long colon) (59), diverticula of the colon (59, 93, 96), orthostatic recurring visceroptosis (98) rectocele (96) and rectal prolapse (93). In addition to structural gastrointestinal manifestations recent research has suggested that patients with JHS are more likely to be diagnosed with functional gastrointestinal disorders (FGID) compared to organic disorders when seeking diagnosis of gastrointestinal symptoms at a tertiary gastrointestinal clinic. The prevalence of diagnosed JHS has been identified as significantly greater in FGID

patients (39%), compared to patients diagnosed with an organic gastrointestinal condition (27.5%) (99). Although JHS was more prevalent in FGID, organic disorders were frequently diagnosed in individuals with JHS, accounting for 38.6% of individuals diagnosed with reflux disorders, 21% of ulcerative colitis cases and 32% of individuals diagnosed with Crohn's disease (99).

FGID can be defined as intermittent or chronic gastrointestinal symptoms, which are not explained by a pathophysiological, biochemical or structural cause (95, 100). In JHS/EDS-HT, symptoms related to FGID where no structural diagnosis have been found include; bloating, nausea, vomiting, reflux, recurrent abdominal pain, constipation, dysphagia, and diarrohea. In a 20yr retrospective study of individuals affected by EDS-HT, 30.3% reported symptoms consistent with irritable bowel syndrome (96). Symptoms not explained by the current pathophysiological understanding of gastrointestinal manifestations in JHS/EDS-HT are referred to as FGID. The role of a dysfunctional autonomic nervous system and the effect of altered connective tissue on the gastrointestinal system in JHS/EDS-HT are not yet fully understood. It is therefore possible that with increasing research and knowledge developing in this area, the exact mechanisms and pathophysiology behind currently unexplained gastrointestinal manifestations in JHS/EDS-HT may become clearer.

Gastrointestinal dysmotility has been associated with JHS/EDS-HT, with reports of altered gastric emptying and colonic transit showing both accelerated and delayed patterns of motility (96). This was supported by a study conducted by Zarate et al in 2010 in which 80% of individuals assessed for gastric emptying (15) showed delay while 100% of individuals assessed for colorectal transit (5) showed signs of abnormal transit (95).

Lifetime gastrointestinal symptom profile in JHS/EDS-HT has demonstrated that symptoms such as dyspepsia, recurrent abdominal pain, Gastro-oesophageal Reflux Disease (GORD) and constipation increase in frequency as an individual ages (97). The severity of JHS/EDS-HT presentation is associated with increased upper and lower GI tract symptoms, with lower GI tract symptoms related to both chronic pain and autonomic symptom burden (94).

Fatigue:

Fatigue is a subjective multifactorial complaint experienced by both healthy individuals and by those affected by a range of health conditions. The presentation of fatigue can be mediated by medical or psychological factors and may result from side effects caused by the medical management of many diseases. The experience of fatigue can be described as a sense of overwhelming tiredness or exhaustion or feeling of lacking in energy, distinct from muscle fatigue or weakness (101). It can present in an acute form as a physiological response, or as a consequence or manifestation of a chronic condition. Severe debilitating chronic fatigue is frequently associated with a range of systemic medical conditions including but not limited to Multiple Sclerosis (102), Rheumatoid Arthritis (103) and Systemic Lupus Erythematosus (104).

Due to the subjective nature of fatigue, fatigue severity is typically assessed using questionnaire-based tools. Research investigating JHS/EDS-HT have utilized the Fatigue Severity Scale (FSS) (57) while general EDS research have employed the Checklist Individual Strength (CIS) (60, 105) to measure fatigue severity, providing comparative data for both tools in this population. The FSS is a 9 item self-report questionnaire, with the FSS mean fatigue severity individual item score of 4 out of a possible 7 (106) or total score of 36/63 (102), generally accepted as the cut-off indicating the presence of significant fatigue. The CIS questionnaire measures 4 aspects of fatigue (subjective feelings of fatigue, motivation, physical activity and motivation) (105), with the fatigue severity determined using the CIS-Fatigue subscale. This subscale includes 8 items with possible scores ranging from 8 to 56. The CIS cut-off for the CIS-Fatigue subscale score is $\geq$ 35/56 which represents a score two standard deviations higher than the mean of healthy individuals (107).

Current research reports fatigue to be one of the most debilitating symptoms experienced across all subtypes of EDS (8, 105, 107) and has been associated with decreased muscle strength (105), sleep disturbances, concentration problems, impaired social functioning, pain severity and lower self-efficacy (107). The prevalence of severe fatigue is greater in the EDS-HT subtype than in the classical subtype of the condition (107) (Table 1.10). Interestingly despite the highest rates of severe fatigue being reported by people with the EDS-HT subtype compared to all

subtypes of EDS, the Villefranche criteria references fatigue as a frequent complaint in only the classical subtype of EDS but not EDS-HT (15).

The incidence of severe fatigue in JHS/EDS-HT has been reported in the literature as ranging from 82 to 100% (9, 108) with the variance in reported incidence likely related to study design and patient selection, the screening tool used to ascertain fatigue severity and the participant comorbidities (Table 1.10). A large cross-sectional study investigated the disease profile of EDS-HT (9), establishing chronic fatigue as the manifestation participants ranked as having the 2nd highest impact on their quality of life, the 6th most frequent feature of the condition and the 2nd most commonly reported systemic feature of the disorder (9).

Table 1.10 Prevalence of Fatigue in JHS/EDS-HT

Study	Sample characteristics	Prevalence of Fatigue (%)	Associated Findings	Conclusions
Rowe et al 1999 (108)	12 participants (6 EDS-HT, 6 Classical EDS) 11 female Median age 15.5yrs	100% Fatigue > 6 months	100% met criteria for CFS Orthostatic Testing: • 9/12 had neurally mediated Hypotension • 7/10 POTS in first 10min of upright posture • 3/10 Isolated POTS	Focus of paper was associations between CFS and orthostatic intolerance. Not JHS/EDS-HT specific.
Castori et al 2010 (59)	21 participants (EDS-HT) 18(85.7%) Female 3(14.3%) Male Mean age 34.8yrs	85.7% Chronic asthenia fatigue		Small cohort of patients. EDS-HT specific.
Voermans et al 2010a (60)	273 Participants EDS: • 162 EDS-HT • 45 Classic EDS • 11 Vascular EDS • 2 Kyphoscoliotic EDS • 53 Type unknown. Mean age 41yrs	92% of participants reported chronic fatigue > 1yr Checklist Individual Strength (CIS) fatigue subscale.	Multiple regression analysis – Pain and Fatigue predictors of Functional Impairment in all EDS patients $R^2 = 0.309$	Concluded pain should be a focus in symptomatic management of EDS. No suggestions regarding fatigue.
Voermans et al 2010b (107)	273 Participants EDS: • 162 EDS-HT • 45 Classic EDS • 11 Vascular EDS • 2 Kyphoscoliotic EDS • 53 Type unkown. Mean age 40.7yrs	Severely Fatigued using the CIS: • Total cohort 77% • EDS-HT 84% • Classic EDS 69%	Statistical significant difference between the presence of severe fatigue in EDS-HT and Classical EDS subtype. Multiple regression analysis for determinants of fatigue ($R^2 = 0.382$): • Sleep disturbances • Concentration problems • Social functioning and social support • Self-efficacy concerning fatigue • Pain 40% of sample – fatigue had greater impact on QOL compared to pain measured using Short Form-36	Suggested addressing predictors of fatigue in the symptomatic management of individuals with EDS.

Voermans et al 2011 (105)	30 participants EDS • 17% EDS-HT Mean age 30	53% Severely fatigued using the CIS Fatigue score	Multiple regression analysis for predictors of fatigue severity (R^2 adjusted 0.27) • Pain severity VAS • Number of muscles with weakness on dynamometry	Pain and reduced muscle strength associated with increasing fatigue severity. No association found between muscle weakness and physical activity. Suggested future longitudinal studies with quantitative measures of physical activity.
Celletti et al 2012 (109)	11 participants EDS-HT Mean age 43.08yrs	Nil % documented	Significantly higher Mean Fatigue Severity Scale (FSS) individual scores compared to controls (6.2 ± 0.9 versus 2.3 ± 0.7; $p > 0.05$) Inverse correlation on gait analysis found between vertical Ground Reaction Force (GRF) and Fatigue severity i.e. decreasing vertical GRF with increasing fatigue severity.	Authors hypothesized reduced GRF may be a consequence of reduced proprioceptive acuity. Suggested further evaluation of predictors of fatigue (identified by Voermans et al 2010b) to determine cause or consequence relationship between fatigue and identify determinants of fatigue.
Celletti et al 2013(57)	42 Participants JHS/EDS-HT 95.2% female Mean age 32.8yrs	88.1% Chronic Fatigue	Mean FSS score 5.47 ± 1.97 Strong correlation between general fatigue severity and kinesiophobia.	Authors proposed a three-phase model of "pain-kinesiophobia-fatigue" whereby musculoskeletal pain leads to fear of movement causing fatigue due to bodily disuse. Suggested individualized multidisciplinary rehabilitation programs to address and prevent chronic pain and deconditioning.

Murray et al 2013 (9)	466 Participants EDS-HT 90% Female Age not stated	82% of participants reported chronic fatigue	Chronic fatigue was the 2nd most frequent Non-MSK manifestation of EDS-HT and was ranked 6th compared to all reported features of the condition. Chronic fatigue was rated by participants as having the highest impact of all non-MSK manifestations of EDS-HT and having the 2nd highest impact on QoL of all reported features of the disorder.	Emphasized the complexity of EDS-HT, with the clinical presentation not limited manifestations relating to joint hypermobility or cutaneous features. Agreed with previous authors that there is a need for improved recognition and management of the condition as a multisystem disorder.

To date there have been only limited studies (57, 109) with small sample sizes, that have focused on investigating fatigue specifically affecting adult individuals diagnosed with EDS-HT, with larger studies investigating fatigue by recruiting individuals with all subtypes of EDS (60, 107). Fatigue severity has been identified as a potential predictor of functional impairment in EDS (60). While two studies have attempted to determine the potential determinants of fatigue severity in the EDS population (105, 107) (Table 1.10). A small study of EDS participants (17% EDS-HT) identified that pain and muscle weakness determined 27% of fatigue severity variance (105). A larger study (59% EDS-HT) identified that sleep disturbances, concentration problems, level of social functioning and level of social support, self-efficacy concerning fatigue and reported pain predicted 38% of the fatigue severity (107).

Particularly in JHS/EDS-HT there is a paucity of research attempting to define the mechanism behind fatigue severity and to identify the predictors of this significant manifestation of the condition. Further specific investigation in this area is likely to progress the knowledge and improve the assessment and management strategies for severe fatigue in JHS/EDS-HT.

Psychological manifestations:

Psychological comorbidities in GJH have been thoroughly investigated and links drawn between joint hypermobility and a range of psychological conditions including anxiety, phobias, depression and somatosensory amplification (Table 1.11). The true incidence and range of psychological manifestations affecting individuals with a definite diagnosis of JHS/EDS-HT is not as well defined. Definitional issues relating to the use of the term Joint Hypermobility Syndrome in Psychiatric literature have occurred with numerous authors using the term Joint Hypermobility Syndrome/Benign Joint Hypermobility Syndrome to describe individuals presenting with GJH as identified using the Beighton criteria (110). This terminology is at odds with the nomenclature recognized by the Rheumatology and Genetics community to describe symptomatic joint hypermobility with systemic manifestations, in the presence of connective tissue disorders as in the case of JHS/EDS-HT.

Table 1.11 Psychiatric research referring to GJH as "JHS",

Study	Sample characteristics	Assessment method	Evaluated for JHS using Brighton Criteria	Diagnosis (JHS or GJH) based on study methodology	Results
Bulbena et al 1988 (111) *	112 subjects "JHS" – sampled from Rheumatology Clinic - joint pain 50 Controls	Beighton score	No	GJH	• 75.9% Anxiety • 36% Simple phobia • 27% Agoraphobia
Bulbena et al 1993 (112) **	114 subjects "JHS" Rheumatology Clinic – joint pain 59 Control subjects	Beighton Score ≥5/9	No	GJH	• 69.3% Anxiety • 29.8% Simple phobia • 11.9% Agoraphobia • 34.2% Panic
Martin-Santos et al 1998 (113) **	99 subjects – newly diagnosed untreated panic disorders and agoraphobia 99 Psychiatric patients - control 64 Medical clinic patients	Beighton Score ≥5/9 to establish diagnosis of "JHS"	No	GJH	• 67.7% of patients with newly diagnosed anxiety disorders had joint hypermobility compared to 10.1% in psychiatric patients and 12.5% in medical patients • Patients with anxiety were 16 times more likely to have joint hypermobility compared to control subjects
Bulbena et al 2006 (114)	182 "JHS" 1123 Control subjects General adult population	Beighton score ≥4/9 men and ≥5/9 for women to establish "JHS" group	No	GJH	• Both men and women in joint hypermobility group significantly higher mean scores on the Fear Survey Schedule compared to control • 43/44 women and 36/39 men rated specific fears significantly greater intensity compared to control group

Ercolani et al 2008 (115)	30 “BJHS” subjects 25 Healthy Control 30 Fibromyalgia	Beighton ≥ 5/9 No musculoskeletal symptoms	No	GJH	• Significantly higher mean scores compared to control for 7/9 scales on the Illness behavior questionnaire including; general hypochondriasis, disease conviction, affective inhibition, affective disturbance, denial, irritability, and Whiteley Index for Hypochondria
Garcia Campayo et al 2010 (116)	55 Untreated patients with panic disorers 55 Fibromyalgia control 55 Healthy Control 55 Psychiatric patient control	Beighton ≥ 5/9	No	GJH	• 61.8% of patients with panic disorders had joint hypermobility, compared to 10.9% in psychiatric control group. • Individuals with joint hypermobility within the panic disorder group were significantly younger (35.2yrs) compared to non-hypermobile (41.7ys)
Mallorqui-Bague et al 2015 (117)	51 non-clinical volunteers.	Beighton score ≥4/9 men and ≥5/9 for women to establish “JHS” group	No	GJH	Participants underwent functional MRI evaluation and completed state and trait anxiety questionnaire: • Joint hyper mobility scores associated with anxiety trait and brain responses in the emotion processing centers of the brain when viewing emotional faces • Suggested hypermobility contributes to vulnerability anxiety and somatic symptoms

* Study conducted prior to publication of the criteria for Hypermobility Syndrome (HMS, AKA JHS) in 1992(45), ** Study conducted prior to publication of the Revised Brighton Criteria(16)

Research clearly investigating connective tissue disorders such as EDS has found that up to 70% of sufferers seek the care of mental health professionals at some stage during their life (118). The specific diagnosis of JHS/EDS-HT has been associated with increased incidence of anxiety, depression, somatosensory amplification (119), and general hypochondriasis (115), with individuals being reported to have a 4.3 times increased lifetime risk of developing any psychiatric disorder compared to the general population (120).

Anxiety has been linked to the presence of joint hypermobility with a number of papers documenting higher rates of anxiety in individuals with Beighton scores of > 5/9 when compared to other psychiatric populations and the general community (Table 1.11). However, the reported incidence of symptoms related to anxiety in individuals specifically diagnosed with JHS/EDS-HT, is less well defined. The prevalence of anxiety affecting individuals with this explicit diagnosis have ranged from 32% (55) to 73% (9, 55). A study that grouped participants diagnosed with all subtypes of EDS demonstrated 74.8% of individuals had levels of anxiety symptoms indicative of "probable" clinical diagnosis (121). Recent findings have reported no definite association between panic disorders and the specific diagnosis of JHS/EDS-HT (120), which is conflict with previous reports linking the presence of joint hypermobility, not specifically associated with an HDCT, with panic disorders (Table 12). Depressive symptoms in the JHS/EDS-HT population have been reported to range between 38% (55) to 69% (9, 55), with symptom levels reaching a "probable" clinical level in 22.4% of those with a general diagnosis of EDS (121). Obsessive Compulsive Disorders have been reported by 10.6% of individuals with JHS/EDS-HT (120). In addition to axis 1 depressive disorders, JHS/EDS-HT have been associated with a 5.8 higher risk of personality disorders compared to unaffected individuals, with a reported incidence of 21% (120).

A potential mechanism identified in both GJH and JHS/EDS-HT which may contribute to psychological distress is the presence of somatosensory amplification, defined as the tendency to perceive somatic sensations as noxious, intense and concerning (122). Somatosensory amplification typically involves a hyper-vigilance and focus on unpleasant sensations, misinterpretation of normal visceral and somatic sensations as pathological or indicating the presence of disease and the tendency to

focus on infrequent sensations (119). It has been hypothesized that somatic amplification may play a role in the increased incidence of anxiety and concern regarding somatic symptoms reported by individuals affected by both GJH and JHS/EDS-HT (117).

The true incidence and type of psychological manifestations associated in JHS/EDS-HT are areas that could be confirmed with further specific research in this patient population permitting the potential to improve the assessment and management of individuals with the condition.

Functional impairments and physical activity participation:

Functional impairment related to reduced mobility, participation in work and daily activities and physical activity have been reported in JHS/EDS-HT. Measurement of functional impairments in EDS-HT using the Sickness Impact Profile (SIP) have identified EDS-HT (N =72) subjects as having comparable overall functional impairment compared to fibromyalgia (FM) patients (N=69) and significantly worse performance on the SIP compared to those with a diagnosis of rheumatoid arthritis (RA) (N= 65) ($p < 0.05$) (7). While specific items on the SIP showed EDS-HT was associated with significantly greater impairments in the physical and psychosocial domains when compared to RA. The domains of the SIP that were associated with the greatest levels of dysfunction in EDS-HT were recreation, hobbies, home management, sleep and rest, alertness and work (7). The specific work related impact of JHS/EDS-HT has been documented in a large cross sectional questionnaire based study including 466 adults diagnosed with JHS (9). Of those who were currently working (55%), 52% of individuals reported they had changed their working role or duties as a result of their symptoms and 82% believed JHS impaired their performance at work (9).

There is a lack of research specifically about the impact of JHS/EDS-HT on participation in physical activity. Rombaut et al 2010 investigated the physical activity, musculoskeletal manifestations and HRQoL in EDS-HT, comparing 32 gender and age matched health controls with a sample of individuals diagnosed with EDS-HT (5). The study identified that individuals affected by EDS-HT participated

in significantly less sports related physical activity ($p < 0.023$) despite spending a comparable period of time performing leisure activities. Specific associations have been demonstrated between objective measures of mobility such as the ambulation sub-scores on the SIP and pain severity in an undifferentiated EDS sample (105). Functional impairments relating to mobility have been documented in females diagnosed with EDS-HT (N=40) when performing the task of sit to stand from a chair compared to unaffected controls. Women with EDS-HT took significantly longer to repeat this task compared to the unaffected control sample ($p < 0.001$) (123). This study also documented significantly reduced lower limb strength and muscle endurance affecting the knee extensors and flexor muscle groups ($p < 0.001$), as well as significantly worse physical function in the EDS-HT group ($p < 0.001$) particularly affecting activities involving bending and walking (123).

Health Related Quality of Life:

The concept of Health-Related Quality of Life (HRQoL) is a multidimensional paradigm, referring to the complex relationship, and interaction between the impacts of disease processes/management, and an individual's physical, social and psychological functioning and wellbeing (124, 125). In a disease process, such as JHS/EDS-HT, where there are significant multisystem manifestations of the disorder, there is significant potential for the condition to result in reduced overall HRQoL.

Studies specifically investigating the HRQoL experienced by individuals affected by EDS have consistently demonstrated lower QoL when compared to healthy samples (107, 121). The domains of HRQoL affected in individuals with JHS/EDS-HT and other subtypes of EDS are not limited to physical functioning or pain but extend to include mental health, social functioning and energy levels (Table 1.12). JHS/EDS-HT specific studies have shown similar levels of disease impact on QOL as in EDS generally. The current research available in JHS/EDS-HT is however limited to pediatric populations or studies with small sample sizes, or minimally affected individuals.

Table 1.12 Health Related Quality of Life:

Study	Sample Characteristics	QOL Instrument	Results	Comments
Rombaut et al 2010 (5)	32 Subjects with EDS-HT 32 Healthy controls Median age of EDS-HT 38yrs	Rand 36-Item Health Survey	Found individuals affected by EDS-HT had significantly lower HRQoL compared to controls, specifically: • Physical functioning • Social functioning • Limitations due to physical problems • Limitations due to emotional problems • Mental health • Vitality • Bodily pain • General health perception • Physical component summary	Small sample size – difficulty drawing causal links. EDS-HT specific.
Voermanns et al 2010 (107)	273 Participants EDS: • 162 EDS-HT • 45 Classic EDS • 11 Vascular EDS • 2 Kyphoscoliotic EDS • 53 Type unknown. Mean age 40.7yrs	Short Form-36	Social functioning scores on the SF-36 contributed to prediction of fatigue severity in EDS sample. Severely fatigued individuals had significantly lower physical functioning scores on the SF-36.	Limitation in generalizing results to JHS/EDS-HT specific populations, as only 59% of participants were EDS-HT subtype.
Berglund et al 2015 (121)	250 subjects with EDS (30% EDS-HT) Mean age 46.15yrs	Short Form-36	Quality of life measures were significantly reduced compared to controls in the domains of: • Physical functioning • Physical role limitation • Bodily pain • General health • Vitality • Social Functioning • Emotional role limitation • Mental health Women reported significantly worse mental health related quality of life compared to men affected by EDS.	Limitation in potential the interpretation of results for JHS/EDS-HT specific populations as only 30% of participants were diagnosed with EDS-HT.

Albayrak et al 2015(126)	115 subjects with BJHS (AKA JHS) 114 Health Control Mean age of BJHS 30.17yrs and 31.81yrs for control group	Short Form-36	BJHS participants had significantly impaired QoL compared to healthy controls in the following domains: • Physical functioning • Physical role limitation • Bodily pain • General health • Emotional role limitation • Mental health • Mental Component summary Pain scores on SF-36 positively correlated with Pittsburgh sleep quality index (PSQI), Beck Depression Inventory (BDI) and total Checklist Individual Strength (CIS). Inverse correlation: • between PSQI and physical and mental components summaries, the physical role and emotional role scores of the SF-36. • between BDI and the mental and physical component summaries, physical function, role physical, role emotional and mental health scores of SF-36 • between CIS score and physical function, role physical , role emotional, physical and mental component summaries scores of the SF-36.	BJHS/JHS specific research. Significant limitation in research - excluded individuals with • Pain > 8/10 VAS • Using analgesia for pain relief • Anti-depressants, • Joint pain related to sprains/dislocations/ fractures limiting the sample population to the minimally affected physically by the disorder.
Pacey et al 2015 (86)	89 children with JHS Mean age 11.5yrs	Pediatric Quality of Life 4.0 Generic core scale Pediatric QL Multidimensional Fatigue Scale (MFS)	Multiple regression analysis to determine predictors of Child-reported HRQoL 74% of variance in score accounted for by: • General fatigue • Sleep/rest fatigue • Pain scores • Stress incontinence symptoms	Pediatric population of JSH – limits the ability to generalize results to adult population.

Manifestations of JHS/EDS-HT such as pain, fatigue severity (8), gastrointestinal symptoms (99), orthostatic intolerance (81) and genitourinary manifestations (85) have been correlated with quality of life measures, with increasing severity of manifestation expression associated with worsening HRQoL.

Given the potential impact of the disorder on HRQoL, further larger studies specifically investigating the overall impact of JHS/EDS-HT on HRQoL and determination of which specific disease manifestations are predictive of HRQoL may allow better assessment and more targeted management of individuals potentially reducing the impact of the disorder.

Progressive disability models of JHS/EDS-HT evolution:

In an attempt to explain the clinical heterogeneity seen in JHS/EDS-HT, particularly when comparing the type and severity of symptoms, overall burden of disease and HRQoL reported by individuals affected by JHS/EDS-HT, a model has been proposed to better define disease progression in the disorder (6, 59, 64). Grahame (2013) described three distinct phases of disease progression in JHS/EDS-HT. The first phase of the disability model is proposed to directly relate to manifestations caused by laxity of the connective tissue, including joint sprains, articular instability episodes, hernias (POP and abdominal hernias) and vascular manifestations such as varicose veins. Phase two is defined by manifestations not specifically related to connective tissue laxity such as amplification of pain, the development of fatigue, deconditioning related to reduced physical activity and kinesiophobia and manifestations associated with autonomic nervous system dysfunction such as gastrointestinal symptoms and POTS. The subsequent expression of psychosocial features such as depression, anxiety, decreased function and HRQoL is indicative of the final phase of JHS/EDS-HT (6). A similar expanded model was developed by Castori et al (2013) with the inclusion sensorimotor manifestations and headaches and the expansion of descriptions relating to fatigue, muscle and visceral manifestations of the JHS/EDS-HT (64) (Figure 1.7).

TABLE IV. Features by Type and Disease Phase in the Joint Hypermobility Syndrome.

Disease "phase"	First	Second	Third
Common age at onset	First decade	Second-third decade	Third-fourth decade
Osteoarticular features	Sprains	Recurrent arthralgias	Chronic arthralgias
	Dislocations	Recurrent back pain	Chronic back pain
	Joint "cracks"	Tenosinovitis	Tendon/ligament degenerations
	Growing pain	Radiographic osteoarthritis/spondylosis	Widespread rigidity
	Occasional back/joint pain	Osteopenia	Osteoporosis
Muscular features	(Post)exertional myalgias/cramps	Recurrent myalgias	Chronic myalgias
	Mild hypotonia	Focal muscle hyperalgesia	Fibromyalgia
			Overt muscle weakness
Sensorimotor features	Delayed motor attainment	Recurrent falls	Allodynia
	Lack of coordination	Dysphagia	Dysesthesias
		Dysphonia	Abnormal reactions to multiple physical stimuli (e.g., bright light, noises)
		Paresthesias	
Headache	Occasional/recurrent single-type headache	Recurrent multi-type headache	Chronic headache(s)
		Mild symptoms of cervical spine pathology	Chronic symptoms of cervical spine pathology
Fatigue	Easy fatigability	Poor sleep quality	Post-exertional malaise
		Post-exertional dyspnea	Disabling morning fatigue
Visceral features	Constipation (or/and diarrhea)	Menses irregularities	Pelvic prolapses/stress incontinence
	Bronchial hyper-reactivity	Dysmenorrhea	Multiple visceral prolapses
	Sensitivity to various foods (e.g., gluten, milk proteins)	Dyspareunia/vulvodynia	Chronic pulmonary insufficiency
	Under/hyperactive bladder	Gastrointestinal functional disorder(s)	Interstitial cystitis

Figure 1.7 Model of disease progression in JHS/EDS-HT(64)

The expanded model lacked the emphasis of the significant psychosocial manifestations of the disorder as being present during the third phase of disease progression. In attempts to target treatment to a particular phase in disease progression, the development of preventative measures based on disease phase was developed (Figure 1.8). The authors acknowledge the need for future prospective studies to ascertain the effectiveness of such a model of intervention in JHS/EDS-HT (64).

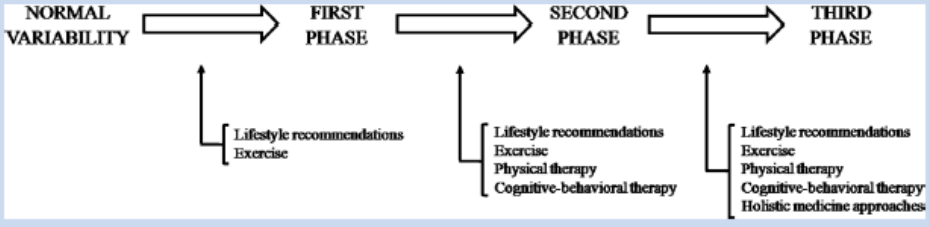


FIG. 5. Stratification of prevention strategies in JHS/EDS-HT in relation to the various transitions among disease phases.

Figure 1.8 Stratification of preventative strategies in JHS/EDS-HT(64)

Current management strategies in JHS/EDS-HT

Despite the recognition of the burden of disease associated with the MSK and systemic manifestations of JHS/EDS-HT there are limited management strategies that have been tried and tested using randomized control studies. A large proportion of published reports relating to management strategies are case presentations or trials involving small sample sizes without control comparison groups. The range of interventional strategies documented in literature relating to the management of JHS/EDS-HT include including splinting/bracing, manual therapy, exercise (both specific and general), cognitive behavioural therapy (CBT), pain management programs, education and proprioceptive exercise programs. The majority of interventions documented are aimed at managing the musculoskeletal manifestations of the disorder such as pain, joint stability and muscle strength with little specific attention on the systemic features of the condition.

In pediatric samples there has been evidence to suggest supervised exercise programs have the ability to decrease pain (127, 128) and improve psychosocial functioning of children participating in the interventions (128). A randomized control trial (JHS, N=57, age 7-16yrs) which compared specific targeted exercise program to a general exercise program treatment group showed that both groups experienced significant reduction in pain levels ($p< 0.001$) but no differences were found between the groups indicating either method of exercise were effective in reducing pain in their cohort of subjects (127). While a RCT investigating physiotherapy lead exercise program, comparing supervised knee exercises, being performed either to neutral or hypermobile ranges, (N = 26, mean age 12.04yrs, diagnosis of JHS) demonstrated significant benefit in terms of psychosocial health, max and mean knee pain scores across both groups with no significant child reported differences between groups (128).

Improvements in psychosocial wellbeing, HRQoL, specific muscle strength, decreased pain and improved proprioception, have been associated with lower limb based exercise programs in the adult population of JHS/EDS-HT (Table 1.13). Despite consistent recommendations in JHS/EDS-HT literature there are limited studies that have investigated the impact of a multidisciplinary approach to the

management of the condition accounting for the myriad of multi-system manifestations. Promising findings have been documented in small trials investigating the efficacy of MDT management of JHS/EDS-HT with significant improvements documented in functional capacity, kinesiophobia, coping mechanisms and functional capacity. However larger randomised control studies are required to investigate the efficacy of combined interventions such as graded exercises programs, CBT strategies to address kinesiophobia, psychological manifestations and coping strategies and pain management strategies, in the management of JHS/EDS-HT.

Table 1.13 Management strategies in Adult JHS/EDS-HT (studies with > 10 participants)

Study	Sample characteristics	Intervention	Results	Comments
Ferrell et al 2004 (129)	20 patients diagnosis of JHS based on revised Brighton (18 completed study) Mean age 27.3	Home based physiotherapy lower limb exercise program: - Closed connectic chain exercises - Hamstring exercises 8 week program – exercise 4/7days per week.	10 patients were measured at commencement and repeated 2-8 weeks later. Significant changes in: - Significant improvement in QoL measured with SF-26 in physical functioning (p= 0.029) and mental health (p= 0.008) summary scores - Decreased pain (p = 0.003) - Increased muscle strength hamstring and quadriceps - Improved proprioception (p < 0.001)	Small sample size. Measurements not taken at a standardized interval. Loss of 8 patients at reassessment.
Sahin et al 2008 (130)	40 individuals with a diagnosis of BJHS Randomised control trial Exercise group 15participants Mean age 25.6yrs Control 25 participant Mean age 27.68yrs	Proprioceptive exercise program for 8 weeks in exercises group.	- Exercise group reported a significant reduction in both activity an resting VAS (Pain) (p<0.05) - No Significant change in VAS (rest or with activity) in control group (p >0.05) - Occupational activity component of the Arthritis Impact Measurement Scale – 2 showed significant improvement in the exercise group (p <0.05) - Proprioception acuity in the knees was improved in the exercise group only (p < 0.001)	Randomised control study. Small sample sizes. Intervention limited to proprioceptive exercises in exercise group.
Bathen et al 2013 (131)	12 women diagnosed with JHS/EDS-HT Mean age 35	Multidisciplinary management of JHS/EDS-HT involving cognitive behavioural therapy (CBT), education and structured exercises program. Two and a half week inpatient program, followed by individual home exercise program (3 months) and 4 days of inpatient retesting and advice.	Significant improvements were found: - Canadian Occupational Performance Measure both performance (p = 0.008) and satisfaction (P = 0.005) measures - Tandem backwards walking (p = 0.006) - Stair walking up (p = 0.004) (down not significant (p = 0.065)) - Calf raises - Kinesiophobia measures (0.022)	No control comparison group. Small sample size.

		Multidisciplinary team: - Physiotherapist - Doctor - Registered Nurse - Social work - Occupational therapy	Pain rating did not show improvements.	
Rahman, Daniel and Grahame 2014 (132)	87 Participants – JHS with pain for greater than 3 months Mean age 35 years	Pain management program (CBT)over 6 weeks (8 days). Multidisciplinary team approach: - Physiotherapist - Rheumatologist - Nurse - Psychology	Significant improvements in measures at 1 month post program: - Self efficacy - Pain catastrophising - Depression - Anxiety - Frustration - Impact on daily life - Average pain intensity 5 months post program – results were remained improved compared to baseline except for pain intensity.	No control comparison for study. Drop out of 25% at 5 month follow-up. Pain levels showed the smallest improvements. Pain catastrophising, self efficacy, frustration and impact on daily life showed greatest improvement at one month follow-up, > 20% improvement compared to baseline measures.

Conclusion:

The complexity and multisystem clinical presentation of JHS/EDS-HT has been exposed significantly over the last 3 decades. Features that have been identified as having significant impact on HRQoL in JHS/EDS-HT include pain, including acute and chronic widespread pain, significant fatigue, gastrointestinal symptoms, orthostatic intolerance and cardiovascular manifestations. There is however an ongoing need to investigate and progress the understanding of the JHS/EDS-HT to help define the full extent, mechanisms and impact of the non-musculoskeletal manifestations of the disorder. In particular, there is a need to better understand the mechanisms contributing to the expression of significant fatigue, psychological, autonomic and gastrointestinal manifestations of the disorder and overall HRQoL.

Chapter Two
Aims and Objectives of the Thesis

Aims of thesis:

The primary aims of this thesis are to improve the knowledge relating to the systemic manifestations of JHS/EDS-HT, particularly relating to fatigue severity, psychological wellbeing and overall HRQoL, to help direct improvements in the diagnostic process and development of targeted management strategies for individuals affected by JHS/EDS-HT.

Objectives of the thesis:

To achieve the aims of this thesis the following objectives were set:

- Define the symptom profile of an adult sample of individuals with JHS/EDS-HT
- Investigate the prevalence and significance of non-musculoskeletal/systemic features of the disorder:
    - Fatigue
    - Psychological manifestations of JHS/EDS-HT
    - Gastrointestinal and cardiovascular
- Determine satisfaction levels associated with current diagnostic and management strategies in JHS/EDS-HT.
- Define the levels of activity participation in JHS/EDS-HT
- Quantify the HRQoL experienced by individuals with JHS/EDS-HT
- Identify potential determinants of:
    - Fatigue severity
    - HRQoL

Chapter Three
Fatigue Severity in Joint Hypermobility Sydrome/Ehlers-Danlos Syndndrome – Hypermobility Type

Study 1: Features that exacerbate fatigue severity in Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome – Hypermobility Type.

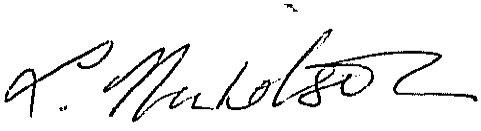
This study has been published in the journal Disability and Rehabilitation:

Krahe AM, Adams RD, & Nicholson LL (2017). Features that exacerbate fatigue severity in Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome – Hypermobility Type. Disability and Rehabilitation (submitted 25 October 2016).

Co-authors' Statement

As co-authors of the paper *Features that exacerbate fatigue severity in Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome – Hypermobility Type*
we confirm that **Anne Krahe** has made the following contributions:

- Conception and design of the research
- Collection and extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the paper and critical appraisal of the content



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Date 3/8/2017

Roger Adams

Date 3/8/2017

DISABILITY AND REHABILITATION, 2017
https://doi.org/10.1080/09638288.2017.1323022

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ORIGINAL ARTICLE

Features that exacerbate fatigue severity in joint hypermobility syndrome/ Ehlers–Danlos syndrome – hypermobility type

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ABSTRACT

Aim: To assess the prevalence, severity and impact of fatigue on individuals with joint hypermobility syndrome (JHS)/Ehlers–Danlos syndrome – hypermobility type (EDS-HT) and establish potential determinants of fatigue severity in this population.

Methods: Questionnaires on symptoms and signs related to fatigue, quality of life, mental health, physical activity participation and sleep quality were completed by people with JHS/EDS-HT recruited through two social media sites. Multiple regression analysis was performed to identify predictors of fatigue in this population.

Results: Significant fatigue was reported by 79.5% of the 117 participants. Multiple regression analysis identified five predictors of fatigue severity, four being potentially modifiable, accounting for 52.3% of the variance in reported fatigue scores. Predictors of fatigue severity were: the self-perceived extent of joint hypermobility, orthostatic dizziness related to heat and exercise, levels of participation in personal relationships and community, current levels of physical activity and dissatisfaction with the diagnostic process and management options provided for their condition.

Conclusion: Fatigue is a significant symptom associated with JHS/EDS-HT. Assessment of individuals with this condition should include measures of fatigue severity to enable targeted management of potentially modifiable factors associated with fatigue severity.

IMPLICATIONS FOR REHABILITATION

- Fatigue is a significant symptom reported by individuals affected by joint hypermobility syndrome/ Ehlers–Danlos syndrome – hypermobility type.
- Potentially modifiable features that contribute to fatigue severity in this population have been identified.
- Targeted management of these features may decrease the severity and impact of fatigue in joint hypermobility syndrome/Ehlers–Danlos syndrome – hypermobility type.

ARTICLE HISTORY
Received 25 October 2016
Revised 11 April 2017
Accepted 21 April 2017

KEYWORDS
Health-related quality of life; hypermobile Ehlers–Danlos syndrome; hypermobility syndrome; mental health; physical activity; orthostatic intolerance

Introduction

Joint hypermobility syndrome (JHS) and Ehlers–Danlos syndrome – hypermobility subtype (EDS-HT) are chronic heritable connective tissue disorders that are characterized by generalized joint hypermobility and a combination of musculoskeletal and multisystem symptoms and signs. The diagnosis of JHS/EDS-HT is made on the phenotypical presentation, together with medical and family history as no genetic markers have as yet been identified [1,2]. There is growing consensus that despite being diagnosed with different criteria (Table 1), JHS (Brighton criteria) [3] and EDS-HT (Villefranche criteria) [4] are indistinguishable conditions and consequently the same phenotypic disorder [1,2,5,6]. The multi-system features of this condition include polyarthralgia, joint instability, skin fragility and hyperextensibility, gastrointestinal and autonomic dysfunction [7] and fatigue [8–11].

Research focusing on the non-musculoskeletal features across all subtypes of EDS has identified fatigue as one of the most debilitating symptoms reported by individuals affected by the disorders [12–14]. Fatigue is widely acknowledged as a disabling symptom affecting health-related quality of life and psychological well-being in a range of chronic health conditions [15–20]. The prevalence of severe fatigue in JHS/EDS-HT has been reported to range from 84% [13] to 88% [21]. To date, research into fatigue severity has predominantly focused on the combined subtypes of EDS, with little research solely investigating the more common subtype of this condition, EDS-HT.

To further evaluate the symptoms and signs of JHS/EDS-HT and better understand the impact of fatigue on individuals with this condition, this study set out to determine the signs and symptoms of JHS/EDS-HT associated with fatigue severity and to identify which features predict an individual's fatigue level. As fatigue has the potential to significantly affect the quality of life in individuals with this condition, is particularly important to determine whether modifiable factors associated with fatigue severity can be identified.

Materials and methods

Participants

Adult participants (16–65 years of age) were recruited via advertising on EDS websites (ConnecTed and EDSAUS) and word of mouth. Respondents who had a diagnosis of JHS or EDS-HT

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Table 3.1 Diagnostic Criteria for EDS-HT (Villefranche Criteria) and JHS (Brighton Criteria)

Villefranche Criteria for EDS-HT [4]	JHS – Brighton Criteria [3]
Major Criteria 1. Beighton ≥ 5/9 2. Skin involvement (hyperextensibility and/or smooth, velvety skin) Minor Criteria 1. Recurring joint dislocations 2. Chronic joint or limb pain 3. Positive family history	Major Criteria 1. Beighton ≥4/9 2. Arthralgia for >3 months in≥ four joints Minor 1. Beighton score 1–3/9 if >50 years old 2. Arthralgia>3 months in 1–3 joints or back pain>3 months 3. Dislocation/subluxation in >1 joint or in one joint on more than one occasion 4. Soft tissue rheumatism > three lesions 5. Marfanoid habitus 6. Abnormal skin: striae, hyperextensibility, thin skin, papyraceous scarring 7. Eye signs: drooping eyelids or myopia or antimongoloid slant 8. Varicose veins or a hernia or rectal or uterine prolapse
The presence of one or more major criteria is either necessary for clinical diagnosis or highly indicative and warrants laboratory confirmation whenever possible. Minor criteria points differentiate between subtypes of EDS but are not sufficient in the absence of major criteria findings for a diagnosis of EDS-HT.	JHS is diagnosed in presence of 1. Two major criteria 2. One major and two minor criteria 3. Four minor criteria 4. Two minor criteria where there is an unequivocally affected first-degree relative JHS is excluded in the presence of Marfan syndrome or EDS (other than EDS-HT).

EDS-HT: Ehlers–Danlos syndrome – hypermobility type; JHS: joint hypermobility syndrome.

were included in this study. Those respondents who had a preexisting diagnosis of Marfan syndrome, Osteogenesis Imperfecta, EDS Type I, II or IV, Stickler's disease or Loeys–Dietz syndrome were excluded from the study. Once consent was gained, a questionnaire was administered and those able to attend in person participated in a physical examination. Ethical approval to conduct this research was granted by The University of Sydney's Human Research Ethics Committee (Protocol number 2012/558).

Questionnaires

Demographic data and information relating to the symptoms and signs associated with connective tissue disorders were obtained. Information regarding previous surgery, use of analgesics and co-morbidities was recorded and structured questionnaires were used to ascertain the self-perceived fatigue, health-related quality of life, mental health, joint hypermobility and activity participation.

Fatigue

The Fatigue Severity Scale (FSS) [17], a nine-item self-report scale with a range 9–63, measured fatigue using both total and mean of individual scores. Higher scores represent greater perceived fatigue. The FSS has previously been utilized to investigate fatigue in JHS/EDS-HT [21], chronic health conditions where fatigue is a significant symptom, including chronic fatigue syndrome, fibromyalgia [16], systemic lupus erythematosus [17], multiple sclerosis [17,22] and Marfan syndrome [23]. Normative FSS values are available for healthy adult populations [17,22]. The FSS has been shown to have excellent internal consistency and high test–retest reliability [22]. A mean fatigue severity individual score of 4 out of a possible 7 [22] or a total score of 36/63 [17] are the cutoffs indicating significant fatigue.

Quality of life

The Assessment of Quality of Life (AQoL)-6D, a multidimensional 20-item instrument measuring self-reported, health-related quality of life was utilized. The instrument assesses six dimensions of health-related quality of life; independent living, mental health, coping, relationships, pain and senses (i.e., sight/smell/touch/hearing/taste). Internal consistency of the four domains is rated as acceptable to good in a community, non-diseased sample (Cronbach's a range: 0.73–0.86), while relationships and senses are rated as questionable to poor respectively [24]. The tool is described as possessing appropriate levels of construct, concurrent and divergent validity [24]. Each dimension is scored between 0.0 and 1.0, with higher scores indicating the better perceived health-related quality of life [25].

Mental health

The psychological well-being of each participant was measured using the Depression Anxiety Stress Scale (DASS-21), a 21-item, self-report measure consisting of three dimensions; depression, anxiety and stress. The DASS-21 has acceptable to excellent internal consistency and normative data have been reported [26,27]. The DASS-21 individual scores were doubled to enable an interpretation of the severity of the individual dimension scores using DASS-42 data [28], a method shown to produce a valid interpretation of the DASS-21 values [26]. A higher score indicates poorer mental health.

Physical activity

The Physical Activity Index is a composite score, with three individual components; intensity (1–5), duration (1–4) and frequency (1–5). The composite score is calculated as Intensity × Duration × Frequency ¼ total score/100. The total score is used to classify an individual's current physical activity participation as sedentary (<20), poor (20–39), fair (40–59), very good (60–80) or high (81–100) [29].

Historical generalized joint hypermobility measure

The Hakim 5 [30] is a five-item self-report questionnaire for identifying hypermobility that requires yes/no responses. Two of the questions relate to hypermobility at specific joints while the remaining three require the participant to attend to historical and general aspects of joint flexibility. The questionnaire is reported to have 83% sensitivity and 89% specificity for diagnosing generalized hypermobility [30]. A positive response to two or more of the five questions results in an accurate diagnosis of generalized joint hypermobility 84% of the time.

Physical examination measures

Those able to attend underwent a physical examination, which included assessment of hypermobility using the Beighton score [31].

Statistical analysis

SPSS (version 23, Chicago, IL) was utilized for data analysis. Descriptive statistics were used to define the study sample. Correlation analysis was performed using Pearson's coefficient (*r*), with the level of significance set at a probability (*p*) value of less than 0.05. Stepwise multiple regression analysis was performed, with fatigue (FSS individual mean score) as the dependent variable, and eight variables representing dimensions of JHS/EDS-HT entered as independent variables. The variables identified in the final model of the multiple regression analysis were viewed as predictors of fatigue severity in this group.

Results

Participant background

Data were available for 117 participants (110 female and 7 male), with a mean age (SD) of 35.0 years (12.1). Fifty-nine participated in both the physical examination and questionnaire component of the study. Participants were asked to record any diagnosis they had received from medical professionals relating to their joint hypermobility (Table 2).

Connective tissue features of JHS/EDS-HT

Table 3 provides the mean (SD) results of hypermobility tests as continuous measures and physical self-report data. Of the subjects who completed the questionnaire, 96.5% met the ?_2/5 cutoff for identification of generalized joint hypermobility using Hakim 5, while 88.1% met the ≥4/9 Beighton cutoff.

Self-report information on musculoskeletal related features of JHS/EDS-HT was collected. Of those who had a history of fractures, 43.8% reported they had suffered a fracture as a result of low force trauma. Joint dislocations occurred during childhood in 48.3% of individuals. Hernias were present in 24.8% of participants.

Fatigue

The cutoff for severe fatigue was met by 79.5% of the cohort. A mean (SD) total fatigue severity score of 48.8/63 (14.5) and individual fatigue score of 5.4/7 (1.6) were recorded. Figure 1 demonstrates the mean severity of reported fatigue of JHS/EDS-HT participants in this study compared to those in studies of other chronic diseases. Fatigue significantly correlated with a range of musculoskeletal, non-musculoskeletal, health-related quality of life and mental health measures (Table 4). The mean (SD) duration of sleep per night was 6.9 h (2.0). Participants answered questions in relation to the quality of their sleep with the following responses; 90% reported not feeling refreshed on waking, 70% were awoken by discomfort, 37% reported snoring, 69% reported difficulty getting to sleep with 66% of this reporting requiring longer than 20 min to fall to sleep on a typical night.

JHS/EDS-HT related autonomic nervous system dysfunction

Autonomic nervous system dysfunction, relating to the cardiovascular and gastrointestinal systems, was reported by 42.2% of participants. Cardiovascular-related autonomic dysfunction had been medically diagnosed in 21.6%, with the specific diagnosis of postural orthostatic tachycardia syndrome in 16.4% and orthostatic intolerance in 5.2%. Dizziness was measured on a visual analog scale (VAS) (0 = "never" and 100 = "often" experiencing dizziness), the mean score (SD) was 73.8 (28.9).

Gastrointestinal complaints that could be attributed to the autonomic nervous system were present in 26.7% of participants. The frequency of passing stools was measured on a scale of 1–6, where 1 represented passing stool more often than once per day and 6 represented less than once per week. The mean (SD) was 2.3 (1.2) representing passing stools "once a day". The medical diagnosis of gastroparesis was reported by 1.7% and irritable bowel syndrome by 15.5% of the sample.

Table 3.2 Specific diagnosis provided by medical professionals related to participant's joint hypermobility.

Diagnosis related to joint hypermobility symptoms/signs	Frequency %
Diagnosis relating to joint hypermobility	
EDS/HT	65% (*n* = 76)
JHS	27% (*n* = 32)
Diagnosed with both JHS and EDS-HT	8% (*n* = 9)
Comorbid diagnosis Fibromyalgia	
(comorbid)	11% (*n* = 13)
Chronic fatigue syndrome (comorbid)	7% (*n* = 8)
Generalized joint hypermobility (comorbid)	7% (*n* = 8)
Osteoarthritis	3% (*n* = 3)
Satisfied with diagnosis and management	42% (*n*=49)

EDS-HT: Ehlers–Danlos syndrome – hypermobility type; JHS: joint hypermobility syndrome.

Table 3.3 The extent of hypermobility and connective tissue related measures in the group.

Connective tissue features	Mean (SD)
Beighton (out of 9)	5.8 (1.8)
Hakim 5 (out of 5)	3.8 (1.1)
Number of painful joints	9.4 (5.3)
Number of painful muscles	3.1 (3.3)
Number of fractures	1.9 (3.5)
Number of dislocations	2.2 (3.3)
Number of connective tissue-related surgeries	1.5 (2.9)
Ease of bruising (100 mm VAS)[a]	65.1 (25.2)
Urinary incontinence (100 mm VAS scale)[b]	37.8 (34.7)

[a]0: hardly at all; 100: extremely easily.
[b]0: never leaking urine on cough/jump; 100: often.
VAS: visual analog scale.

Table 3.4 Correlation (Pearson's *r*) between mean fatigue score and hypermobility, joint and muscle pain, physical activity, sleep duration, mental health, QoL, dysautonomia and symptoms of urinary incontinence.

	Correlation with fatigue
Hakim 5 total score	0.314**
Number of joints affected by pain	0.346**
Number of muscles affected by pain	0.279**
Physical activity index total composite score	−0.438**
Average hours/night sleep	0.047
DASS-21 Depression	0.286**
DASS-21 Anxiety	0.385**
DASS-21 Stress	0.158
AQoL relationship dimension	−0.615**
AQoL coping dimension AQoL	−0.570**
pain dimension	−0.526**
AQoL total score	−0.712**
Dizziness VAS	0.350**
Incontinence VAS	0.191*
Stool frequency	0.146

DASS: depression anxiety stress scales; AQoL: assessment of quality of life instrument; VAS: visual analog scale.
*indicates $p ::: 0.05$, **indicates $p ::: 0.005$.

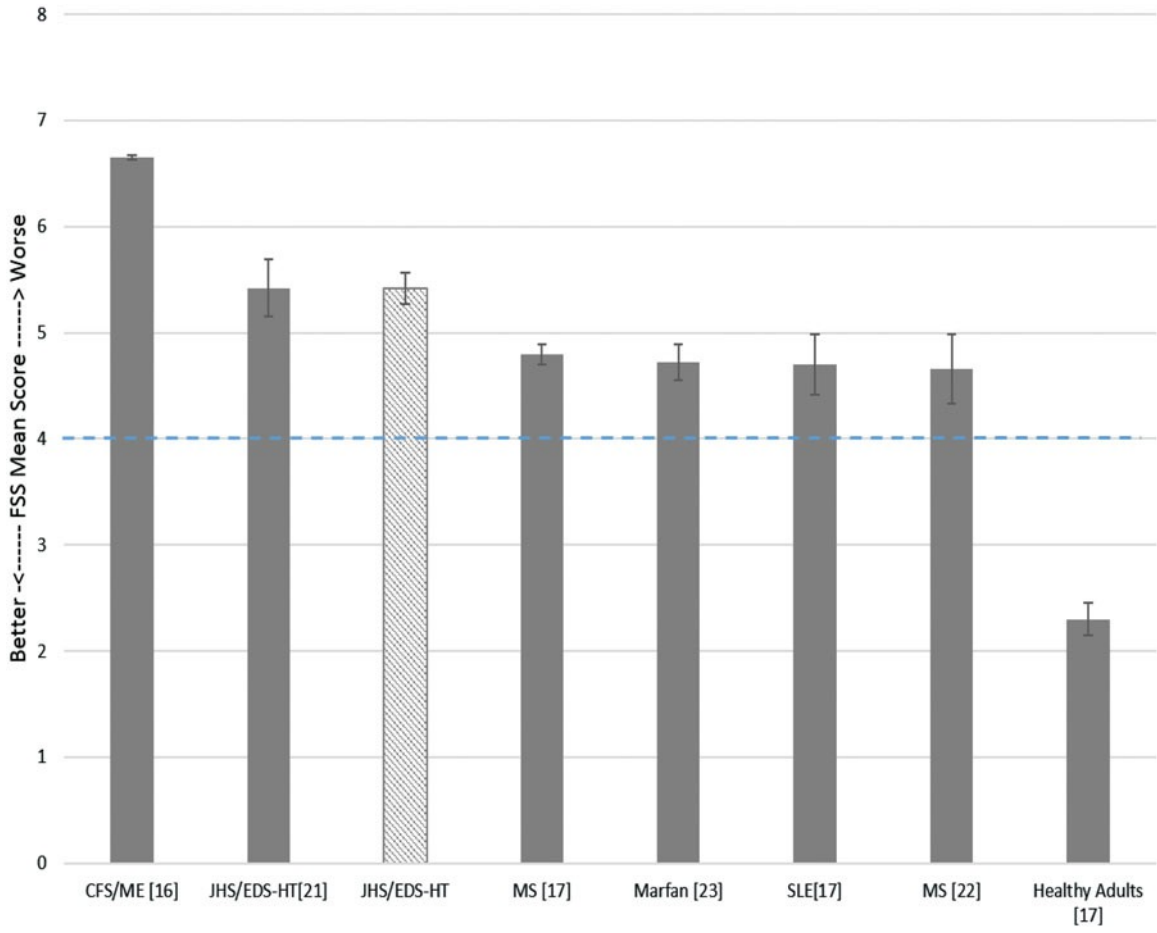

Figure 3.1. Mean individual fatigue score for JHS/EDS-HT in the current study, *n* =117 (diagonally hatched bar) compared to healthy adults and people with other chronic diseases. The dashed horizontal line represents the criterion for severe fatigue of > 4/7. Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) (*n* = 123) [16]; multiple sclerosis (MS) (*n* = 25), systemic lupus erythematosus (SLE) (*n* = 29) and healthy adults (*n* = 20) [17]; JHS/EDS-HT (*n* = 42) [21]; multiple sclerosis (MS) (*n* = 188) [22]; Marfan syndrome (*n*=73) [23]. FFS: fatigue severity score; EDS-HT: Ehlers–Danlos syndrome – hypermobility type; JHS: joint hypermobility syndrome.

Quality of life and mental health

The mean (SD) total AQoL score was 0.61/1 (0.14) and the individual component scores were: independent living 0.64 (0.22), relationships 0.68 (0.19), mental health 0.59 (0.15), coping 0.50 (0.17), pain 0.41 (0.22) and senses 0.81 (0.11). Figure 2 compares these total and composite scores with normative data.

The DASS-21 was utilized to evaluate the dimensions of an individual's mental health. The individual dimension scores of depression, anxiety and stress were doubled as were the total DASS-21 scores [26], so that they could be compared with normative data using the DASS-42. The mean (SD) depression score was 10/42 (8.7), anxiety 9.35/42 (7.2), stress 15.7/42 (9.1) with the combined total score 35.0/126. These mean scores, normative values for a healthy adult population [26] and mean scores for a chronic pain cohort are presented in Figure 3.

Physical activity

Mean physical activity participation resulted in a mean Physical Activity Index score of 25.5/100, which placed the cohort in the "poor" category with respect to their current activity levels. Of the cohort, 50% were sedentary, 28% poor, 10% fair and only 12% very good or highly active.

Multiple regression analysis

A stepwise multiple regression analysis was conducted with the Mean Fatigue Severity Score as the dependent variable and eight independent variables entered; Hakim 5 (self-perceived joint hypermobility), DASS-21 depression total score (mental health), dizziness VAS (cardiovascular/orthostatic autonomic symptoms), frequency of stool motions (gastrointestinal related symptoms), pain dimension of the AQoL, relationship dimension of the AQoL (related to participation in community/family), perceived satisfaction with diagnosis and treatment options provided by treating practitioners (dichotomous choice where "0" represents dissatisfied and "1" represents satisfaction) and Physical Activity Index composite score (physical activity participation). Using the method of simple regression imputation to account for missing data (DASS-21 Depression *N*=0, AQoL relationship dimension *N*=11 and AQoL pain dimension *N*=11) 3% of the total data were replaced [32]. The regression analysis produced a model that accounted for 52.3% of the variance in the FSS mean individual score, with five predictors of fatigue severity. The resulting regression equation for predicting an individual's mean FSS was:

Mean Fatigue Severity Score = 6.5–3.7 (AQoL Relationship Dimension score) + 0.012 (Dizziness VAS) – 0.017 (Physical Activity Index Total Score) – 0.54 (Patient Satisfaction) + 0.32 (Hakim 5 Score).

Discussion

From the examination of possible determinants of fatigue severity in individuals who met the diagnostic criteria for JHS/EDS-HT, five predictors of fatigue severity were identified: the self-perceived extent of joint hypermobility, orthostatic dizziness, participation in personal relationships and community, physical activity and satisfaction with medical management and treatment options offered by health professionals. This set of predictor variables for fatigue severity represents features that collectively challenge an individual's capacity to cope with their condition. Although the measure of historical joint hypermobility (the Hakim 5 score) is not modifiable, the identification of potentially modifiable predictors of fatigue gives researchers and clinicians the prospect of developing and improving treatment and referral pathways for the management of fatigue in this clinical population. This study corroborates findings of previous research identifying fatigue as a significant clinical symptom for people with JHS/EDS-HT. The prevalence of severe fatigue in this sample of the JHS/EDS-HT was 79.5% when measured using the FSS, a figure comparable to previous reports of prevalence in this population ranging from 84% [13] to 88% [21]. The proportion of the current sample who reported significant fatigue was not significantly lower compared to the cited studies (both $p > 0.22$). Previous research, which has investigated fatigue severity in the setting of EDS, has taken a general approach to the condition by including all five subtypes of EDS in the cohort sample. Multiple regression analyses performed in these studies were able to account for 38% [13] and 27% [12] of the variance in the FSS, values less than the current sample where 52.3% of the variance in the FSS was accounted for by five variables. The relatively homogenous sample in the current study, including only JHS/EDS-HT subjects, may explain the improved ability to identify features that account for fatigue severity.

In terms of outcomes, there are similarities between the current study and those previously undertaken, with pain severity identified as significantly associated with fatigue severity [12,13]. The current study did not, however, identify pain severity as a predictor of fatigue in this population. Disease-related features, such as higher self-perceived hypermobility and reduced social functioning, ranging from participation in the family to community-based activities, were predictive of higher levels of fatigue in the current study and that of Voermans et al. (2010) [13]. Further research on the construct validity of the AQoL-6D in chronic pain cohorts is required to determine the internal consistency of the tool.

The current study has identified three further predictors of fatigue severity in addition to those previously described. Results indicate that physical activity participation, orthostatic dizziness associated with heat and exercise, and satisfaction with the diagnosis and management offered by health professionals, also

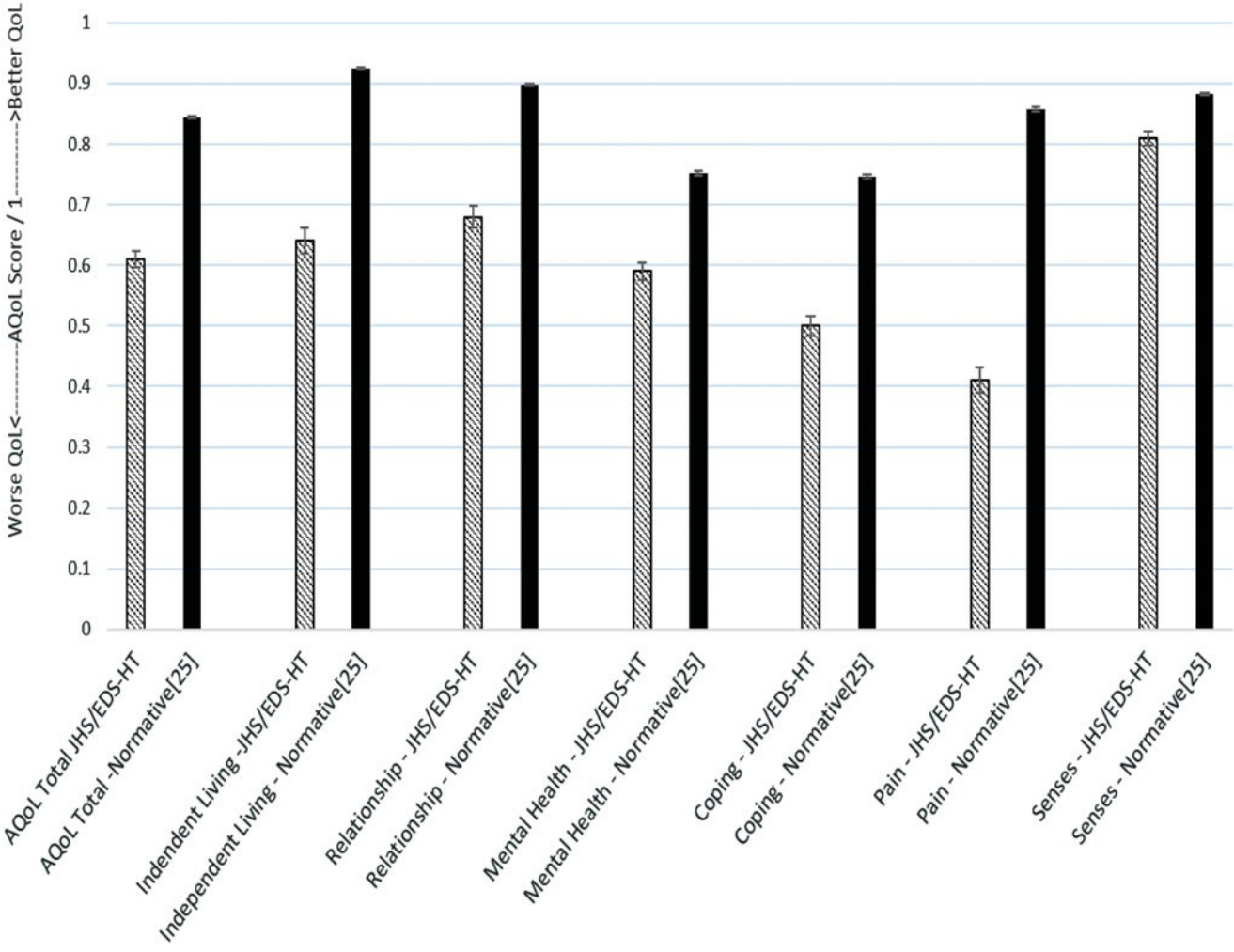

Figure 3.2 Mean AQoL total score and means of the six component scores for JHS/EDS-HT participants in the current study, $n=106$ (diagonally hatched bars) compared to normative scores. [25] Normative values for AQoL-6D ($n=2731$). AQoL-6D: assessment of quality of life – 6 dimensions; EDS-HT: Ehlers–Danlos syndrome – hypermobility type; JHS: joint hypermobility syndrome.

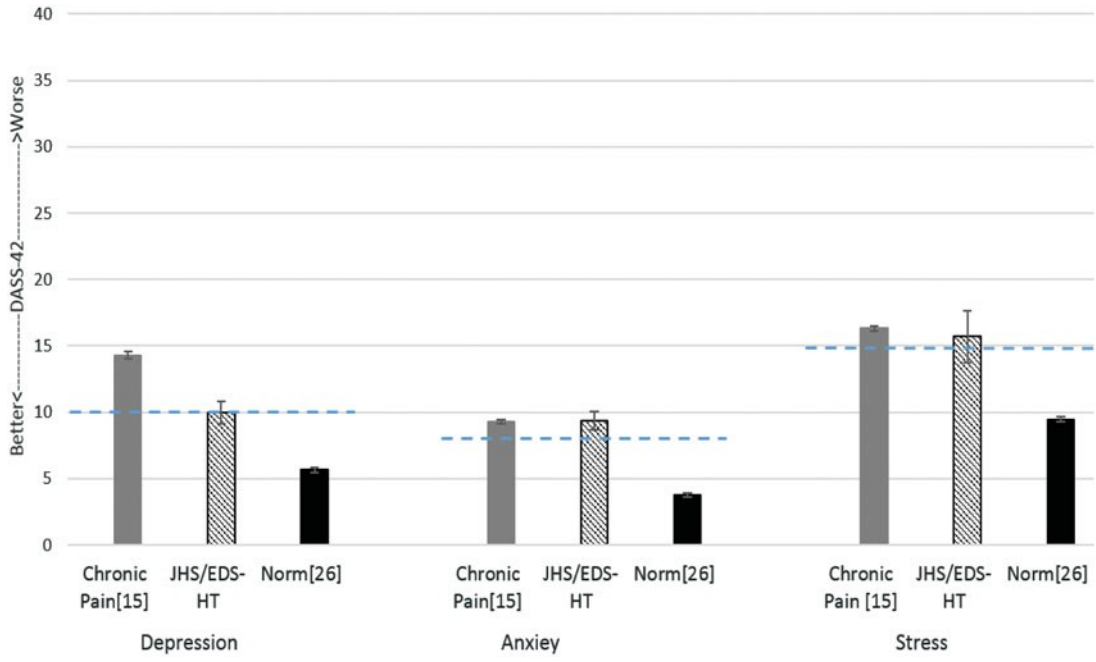

Figure 3.3 Mean DASS 21 dimensional scores for JHS/EDS-HT participants, n = 107 (diagonally hatched bars), with comparative data; each dimension score range is 0–42. The dashed horizontal lines represent the cutoff scores for mild symptom severity for depression (10), anxiety (8) and stress (15) [28]. [15] Chronic pain population DASS Depression dimension (n=2445) and DASS anxiety dimension (n=2421); [26] normative data for DASS-21 (n=1794). DASS-21: Depression Anxiety Stress Scales, 21 item version; EDS-HT: Ehlers–Danlos syndrome – hypermobility type; JHS: joint hypermobility syndrome; norm: normative.

contribute to the prediction of fatigue severity in JHS/EDS-HT participants.

While Voermans et al. (2011) found no association between activity participation and fatigue severity, in the current cohort physical activity participation was a determinant of FSS scores, with lower activity participation, measured using the composite Physical Activity Index score, associated with higher levels of fatigue. This discrepancy may be due to the heterogeneity of the sample in Voermans et al.'s study, where only 17% of their EDS participants had EDS-HT [12].

Orthostatic intolerance is a condition related to autonomic nervous system dysfunction and symptoms include dizziness, palpitations and syncope. Episodes are typically precipitated by orthostatic changes and can be exacerbated by physical exertion and heat [33]. Orthostatic intolerance is a significant non-musculoskeletal complaint which has been associated with JHS/EDS-HT and prevalence of symptoms has been reported as up to 78% of individuals with a diagnosis of JHS [34]. Fatigue has previously been linked to postural orthostatic tachycardia syndrome, a form of orthostatic intolerance [35], with 58% of individuals with JHS-related postural orthostatic tachycardia syndrome suffering from clinically significant fatigue [36]. The findings of the current research showed that 22% of participants reported symptoms related to orthostatic intolerance and its contribution to fatigue severity in the multiple regression supports previous research linking orthostatic intolerance to fatigue [36]. A higher frequency of dizziness related to heat, exercise and or postural change was significantly correlated with and a predictor of, fatigue severity. Orthostatic intolerance is a potentially modifiable condition, both pharmacologically and non-pharmacologically [33].

The high level of dissatisfaction with the diagnostic process and treatment options provided by practitioners observed here is not an isolated finding in JHS/EDS-HT-related research. Qualitative research has revealed that individuals with a diagnosis of JHS generally feel that their condition is poorly understood, and many report lengthy delays in obtaining a diagnosis [37]. Patients diagnosed with EDS have also described experiences with health professionals that have left them feeling ignored and on some occasions, they report being assigned psychiatric or psychological explanations for their symptoms, with resultant anxiety concerning the management of their condition [38].

The acceptance of JHS/EDS-HT as a pathological and multisystem disorder is a potential obstacle to appropriate diagnosis and management. One study found that only 39% of UK rheumatologists recognized hypermobility syndrome (synonymous with JHS) as a pathological entity, only 6% of respondents considering non-articular signs in its diagnosis [39]. Another study reported less than 25% of USA physical therapists considered JHS to be a systemic condition with only 13% identifying fatigue as a significant feature of the condition [40]. Only 36% of these therapists utilized the Beighton score and 27% used the Brighton criteria [40]. The knowledge and beliefs of health care practitioners relating to the tools utilized in the diagnosis of JHS/EDS-HT and the presence of non-articular signs and symptoms associated with the disorder, highlight an opportunity for education of medical and allied health students and practitioners regarding the condition, thereby facilitating the development of timely and appropriate management plans. A reduction in the lengthy delay that many patients experience in obtaining a diagnosis and an improvement in the specificity of subsequent management options may improve patients' overall satisfaction with the diagnosis, treatment and management options provided by practitioners, and thereby have some impact on their fatigue.

The psychological symptoms evident in the current cohort are comparable with those reported by patients seeking tertiary pain management services for chronic pain [15]. Previous research has identified that individuals with JHS/EDS-HT have higher incidences of anxiety, depression, panic-agoraphobia and resultant utilization of anti-anxiety medication compared to non-affected individuals [41]. The current study found a significant association between psychological symptoms and fatigue. It is, however, pertinent to acknowledge that the multiple regression analysis applied to the

current cohort did not find that psychological factors relating to depression predicted fatigue severity.

It is relevant to consider the generalizability of the results of this study to the population of persons with JHS/EDS-HT. The ratio of female to male participants was high; however, this reflects the gender imbalance commonly seen clinically in this population. The study protocol, recruiting participants through two online support group websites, may have resulted in sampling bias. It is possible that the members of such a group do not fully represent the entire population of people diagnosed with the condition. A further limitation of all research on JHS/EDS-HT is the lack of clear diagnostic criteria.

The results of the current study highlight directions for improvements in the diagnosis and management of individuals affected by JHS/EDS-HT, and in particular the management of fatigue, a significant feature of the disorder. The identification of four potentially modifiable predictors of fatigue suggests the benefits of screening of individuals with JHS/EDS-HT for fatigue and assists in the selection of management options for symptoms and signs shown to determine fatigue severity. Identification of modifiable predictors of fatigue will assist with early referral to appropriate health practitioners. The findings of the current study support the future inclusion of management strategies to address; levels of physical activity participation (physiotherapists and exercise physiologists); coping strategies to improve participation in community and family interactions (clinical psychologists) and investigation and management of orthostatic intolerance (cardiologists). Given the inadequate recognition of the condition by health professionals, professional education particularly for primary practitioners (including but not limited to rehabilitation specialists, geneticists and rheumatologists) regarding the complex diagnosis of the disorder and the scope of potential management strategies, may assist in the management of fatigue severity in this population. The combination of predictors identified highlights the need for a multidisciplinary approach to optimize the management of JHS/EDS-HT, supporting previous research advocating such an approach to the overall management of this condition [8,14,42–44].

Conclusion

The current findings regarding JHS/ED-HT can direct practitioners towards potential interventions that may help to improve an individual's fatigue levels and as a consequence, their health-related quality of life. Further research will determine if the identification and management of the recognized predictors of fatigue can, in fact, result in decreased fatigue severity in this population.

Acknowledgements

The authors acknowledge the assistance of Dr Bronwen Ackermann in the development of a standardized testing protocol.

Disclosure statement

The authors report no conflict of interest.

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Chapter Four
Health-Related Quality of Life in JHS/EDS-HT

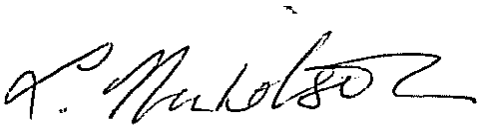
Study 2: Features that determine Health-Related Quality of Life in individuals affected by Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome-Hypermobility Type.

A paper based on the study in this chapter will be submitted for consideration for publication.

Co-authors' Statement
As co-authors of the paper "*Features that determine Health-Related Quality of Life in individuals affected by Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome-Hypermobility Type.*"

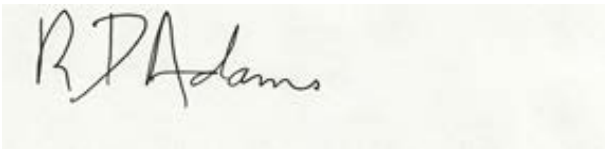
we confirm that **Anne Krahe** has made the following contributions:

- Conception and design of the research
- Collection and extraction of data
- Analysis and interpretation of the findings
- Drafting and revising of the paper and critical appraisal of the content



Leslie Nicholson

Date 3/8/2017



Roger Adams

Date 3/8/2017

Features that determine Health-Related Quality of Life in individuals affected by Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome-Hypermobility Type.

Abstract:

Aims:

To identify the features of Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome-Hypermobility Type (JHS/EDS-HT) that are associated with Health-Related Quality of Life (HRQoL) and to determine if there are modifiable predictors of HRQoL in this condition for which targeted management strategies could be developed.

Methods:

In a cross-sectional study of individuals affected by JHS/EDS-HT, questionnaires were used to obtain information on; symptoms and signs related to JHS/EDS-HT, fatigue, HRQoL, mental health, physical activity participation and sleep quality. Multiple regression analysis was performed to identify predictors of HRQoL in this population.

Results:

HRQoL obtained using the Assessment of Quality of Life-6 Dimension measure was significantly reduced in the 106 participants with JHS/EDS-HT, compared to normative data. HRQoL was significantly correlated with a range of manifestations of JHS/EDS-HT. Of these, fatigue was found to have the strongest relationship with overall HRQoL ($r = -0.712$, $p < 0.005$), while depression, anxiety, current levels of physical activity participation, the number of cardiac/vascular manifestations and number of joints affected by pain were all moderately correlated with HRQoL. With the moderately correlated features entered as independent variables, multiple regression analysis identified that the number of joints affected by pain, the current level of physical activity and depression symptoms were predictive of 54.9% of the overall variance in HRQoL reported by participants of the study.

Conclusion:

Overall HRQoL is significantly lower than normal in individuals with JHS/EDS-HT. Information about the key contributors to HRQoL in this condition gives clinicians and researchers options for future investigation of interventions aimed at improving the lived experience of those affected by the disorder.

Introduction:

Ehlers-Danlos Syndrome – Hypermobility Type (EDS-HT) and Joint Hypermobility Syndrome (JHS) are connective tissue disorders where joint hypermobility is a major diagnostic feature. Despite being diagnosed using different criteria, EDS-HT by the Villefranche Criteria (1) and JHS by the Brighton Criteria (2), the two conditions are increasingly referred to as indistinguishable (3, 4) (Table 4.1). Musculoskeletal symptoms, such as joint hypermobility, instability, and arthralgia, form the basis of the diagnostic criteria for the conditions, however individuals affected by the disorder can experience a range of systemic symptoms, including gastrointestinal (5) and autonomic nervous system dysfunction (6), fatigue (7-10), mental health conditions, anxiety and depression (11), and genitourinary complaints (12).

Historically, there has been a disconnection between the experience of individuals affected by JHS/EDS-HT and the infrequent recognition by the involved health professions of the condition as a systemic multidimensional disorder, rather than as an isolated musculoskeletal condition (13, 14). With increasing research on the features of JHS/EDS-HT, it is becoming clear that the condition not only has significant musculoskeletal and systemic manifestations, but also has a significant detrimental effect on health-related quality of life (HRQoL) (15), causing substantial disease-related morbidity (16).

Research has demonstrated that both the paediatric and adult populations affected by JHS/EDS-HT have globally-reduced HRQoL. Specific associations have been drawn between HRQoL and systemic features including fatigue (17-19), mental health (20), genitourinary (12, 21) and autonomic dysfunction (10), and gastrointestinal symptoms (22). The overall burden of the disease in the adult population of JHS has been found to be similar to that in patients affected by Fibromyalgia, and greater than that for individuals diagnosed with Rheumatoid Arthritis (23). Research focusing on JHS in the paediatric population has identified the severity of pain, fatigue, and stress incontinence as predictors of HRQoL (24). There is a need to replicate and extend this research to the adult population in order to appropriately identify and manage factors that contribute to HRQoL and potentially decrease the burden of the disease on both the individual and the community.

Given the multifactorial nature of JHS/EDS-HT, any single intervention is unlikely to significantly improve overall HRQoL. Therefore, the aims of this study were to identify the features of JHS/EDS-HT that are associated with HRQoL and to determine if there are modifiable predictors of HRQoL in this population, to enable the development of targeted management strategies.

Table 4.1 Diagnostic criteria for EDS-HT and for JHS

Villefranche Criteria for EDS-HT (1)	JHS – Brighton Criteria (2)
Major Criteria **3. Beighton ≥ 5/9** **4. Skin involvement (hyper extensibility and/or smooth, velvety skin)** **Minor Criteria** **4. Recurring joint dislocations** **5. Chronic joint or limb pain** **6. Positive family history**	Major criteria 3. Beighton ≥ 4/9 4. Arthralgia for > 3 months in ≥4 joints Minor criteria: 9. Beighton score 1-3/9 if >50yrs old 10. Arthralgia > 3 months in 1-3 joints or back pain >3 months 11. Dislocation/subluxation in > 1 joint or in one joint on more than one occasion 12. Soft tissue rheumatism ≥ 3 lesions 13. Marfanoid habitus 14. Abnormal skin: striae, hyper extensibility, thin skin, papyraceous scarring 15. Eye signs: drooping eyelids or myopia or antimongoloid slant 16. Varicose veins or hernia or rectal or uterine prolapse
Diagnosis of EDS-HT suggested when: **One or more of the major criteria present.** **Minor criteria points differentiate between subtypes of EDS but are not sufficient in the absence of major criteria findings for a diagnosis of EDS-HT.**	JHS is diagnosed in presence of 5. Two major criteria 6. One major and two minor criteria 7. Four minor criteria 8. Unequivocally affected first degree relative in the absence of Marfan or EDS (other than EDS-HT)

Methods:

A cross-sectional cohort study was undertaken. Recruitment of adult participants (16-65 years of age) was undertaken by advertising on Australian based EDS websites (ConnecTed and EDSAUS) and by word of mouth. Participants were recruited between 2012 and 2014. Individuals with a pre-existing diagnosis of Marfan Syndrome, Osteogenesis Imperfecta, Ehlers-Danlos Syndrome (Type I, II or IV), Stickler's disease or Loeys-Dietz Syndrome were excluded from the study. Participants were included in this study if they had a diagnosis of either JHS or EDS-HT. Once volunteers were consented to participate in the study, a questionnaire was submitted and returned by mail or email. Any responses that were not clear were addressed in further email communication or by phone. The University of Sydney's Human Research Ethics Committee granted ethical approval to conduct this research (Protocol number 2012/558).

Self-Report data:

All participants completed the questionnaire component of the study, providing demographic data and information relating to symptoms associated with JHS/EDS-HT. This included data relating to the presence of joint pain and instability, muscle pain, fracture history, connective tissue/cutaneous features, urinary incontinence (measured on a visual analogue scale (VAS) where 0= never leaking urine on cough/jump to 100 = often leaking urine) and dysautonomia symptoms related to the cardiovascular (Postural Orthostatic Tachycardia syndrome, orthostatic intolerance, orthostatic palpitations, fatigue and dizziness) (16, 25, 26) and gastrointestinal systems (nausea, diarrhoea, constipation, dysmotility of the gastointestinal tract) (27, 28). Orthostatic dizziness was measure on a VAS ((0 = "never" and 100 = "often" experiencing dizziness associated with heat/change in position/participation in exercise). Information regarding co-morbid medical conditions, previous surgery and sleep quality and duration was also recorded. Structured questionnaires were used to ascertain HRQoL, current mental health status, self-perceived joint hypermobility, physical activity participation and fatigue severity.

Health Related Quality of Life:

To establish self-reported HRQoL the AQoL-6D, a six dimension, 20-item instrument was used. The dimensions measured by the instrument include independent living, mental health, coping, relationships, pain and senses (i.e. sight/smell/touch/hearing/taste). Each dimension is scored between 0.0 and 1.0, where a higher score indicates greater perceived HRQoL (29). Adult population normative data is available for comparison (29).

Mental Health:

The Depression Anxiety Stress Scale 21 (DASS-21) was used as an indicator of the psychological wellbeing of each participant. The DASS-21 is a 21-item, self-report tool incorporating the three dimensions of depression, anxiety and stress. Each dimension is assessed with 7 questions; the score range possible for each dimension is 0-21. The total score range for the combined dimensions is 0-63. To interpret the severity of each dimension, individual scores are doubled to enable use of DASS-42 normative data, allowing the comparison of symptom severity to "normal" in each

category (30). A higher score indicates poorer mental health.

Physical Activity:

Current level of physical activity participation was measured using the Physical Activity Index (PAI), giving a composite score, with three individual components; Intensity (1-5), Duration (1-4) and Frequency (1-5). The total score was calculated using the equation, Intensity x Duration x Frequency = Total Score /100, with activity participation classified as; sedentary (<20), poor (20-39), fair (40-59), very good (60-80) and high (81-100) (31).

Self-perceived Hypermobility:

The Hakim 5-part questionnaire (32) is a 5 item self-report tool for identifying historical generalized joint hypermobility (GJH). A score of ≥2/5 is required for a diagnosis of GJH, and this has 84% diagnostic accuracy (32).

Fatigue

Fatigue severity was assessed using the Fatigue Severity Scale (FSS) (33), a nine item, self-report scale with a score range of 9 – 63, whereby higher scores represent greater levels of fatigue. The mean individual score was utilized to compare values to normative FSS data (healthy adult population) (33, 34) and FSS mean scores reported in JHS literature (35). A mean FSS individual score of ≥4/7 (34) or a total score of ≥36/63 (33) are accepted as the cut-off values indicating the presence of significant fatigue.

Sleep measures:

Sleep quality and quantity (hours/night) was measured using a set of specific questions and the creation of a composite score to quantify overall sleep quality. The questions contributing to the composite score were; does discomfort relating to your joint hypermobility wake you, are you un-refreshed on waking, do you snore, do you experience difficulty getting to sleep, if so does it take longer than 20min. Each positive response was allocated 1 point with a maximum score of 5/5 possible, with higher scores indicating reduced self-reported sleep quality.

Statistical analysis:

SPSS (Version 23) was utilized for data analysis. Descriptive statistics were used to define the study sample and independent t-tests were used to compare means of AQoL-6D normative data (29) with those of the study population. Correlation analysis was performed using Pearson's Coefficient (r) to determine the extent of the relationship between variables. Stepwise multiple regression analysis was performed, with the AQoL-6D mean total score as the dependent variable, and eight variables representing dimensions of JHS/EDS-HT likely to affect HRQoL entered as independent variables. The variables identified in the final model of the Multiple Regression Analysis (stepwise method; probability of F in at 0.05 and out at 0.10) were viewed as predictors of HRQoL in the study population. Level of significance was set at a probability (p) value of less than 0.05.

Results:

Participants:

One hundred and six individuals (99 female, 7 male), with a mean (SD) age of 35.64 years (11) met the inclusion criteria and participated in the study (see figure 4.1). Characteristics of the study population can be found in Table 4.2. The specific diagnosis was EDS-HT in 68% and JHS in 25% of study participants, while 7% reported both diagnoses. The prevalence of dissatisfaction with the diagnostic process and management options they were provided was 61.4% of the cohort.

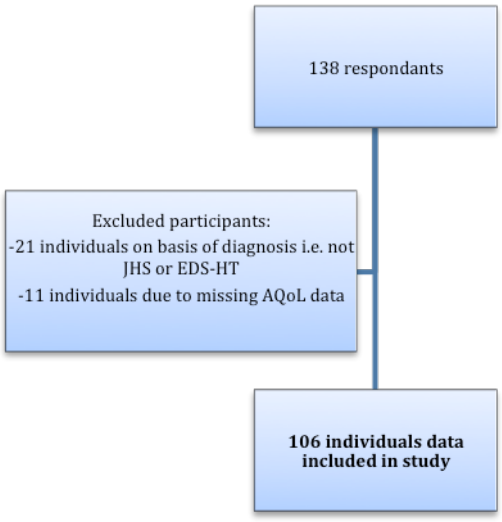


Figure 4.1 Study Population flow chart

Table 4.2 Reported features associated with JHS/EDS-HT

	Mean (SD)
Hakim 5 (/5) (n =106)	3.8 (1.2)
No. Painful Joints (n =106)	10 (5.0)
No. JHS/EDS-HT related Surgeries (n =105)	1.7 (3.)
Individual FSS (n =106)	5.5 (1.6)
PAI total score (n =106)	24.5 (20.5)
Hours Sleep/night (n =103)	6.9 (2.1)
DASS Depression (/42) (n =106)	10 (8.6)
DASS Anxiety (/42) (n =106)	9.3 (7.2)
DASS Stress (/42) (n =106)	15.7 (9.1)

Disease specific data:

Polyarthralgia (≥ 4 painful joints) was present in 88.7%, while soft tissue pain affecting ≥ 3 regions was present in 46.2% of respondents. Non-musculoskeletal features of the Brighton Criteria included hernias in 25.5% and genitourinary prolapse in 3.8% of participants, skin abnormalities in 44% (e.g. thin/stretchy/abnormal scarring) and 45.7% of participants reported being shortsighted.

Self-reported urinary incontinence, measured on a visual analogue scale, revealed a mean (SD) of 36.9 (34.5) while 3.7% of the cohort had undergone surgery for genitourinary conditions.

The prevalence of systemic and musculoskeletal features associated with the disorder are presented in Figure 4.1. Significant fatigue was present 81% of the cohort and was the most prevalent systemic feature of the disorder, second only to arthralgia as the most widespread of all manifestations of JHS/EDS-HT in this population. Features of autonomic dysfunction relating to the cardiovascular system were present in 30.5% of participants, with 17.1% having a specific medical diagnosis of Postural Orthostatic Tachycardia Syndrome, while the mean (SD) VAS score for dizziness was 74.2 (28.9). Gastrointestinal symptoms (e.g. regular diarrhoea/ constipation / stomach upset including diagnoses of gastroparesis /Irritable Bowel Syndrome /Crohn's disease) were reported by 28.6% of the cohort.

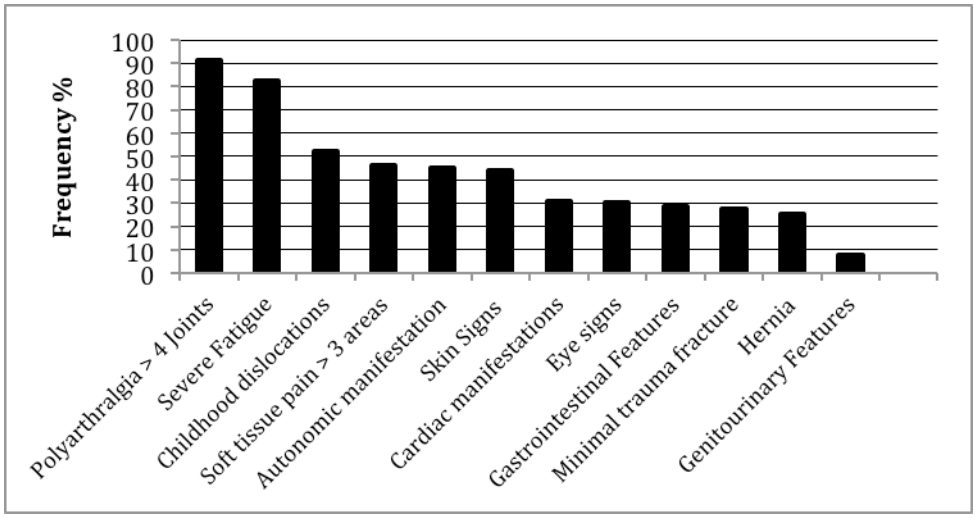


Figure 4.2 Prevalence of musculoskeletal and non-musculoskeletal manifestations of JHS/EDS-HT.

The mean DASS-21 depression, anxiety and stress dimension scores are reported in Table 4.2, while the frequency of each dimension and severity of symptoms reported by participants can be found in Figure 4.2. Analysis of the subscales of the DASS-21 revealed the severity of symptoms reported in each dimension. On the depression subscale, 18% had mild, 18% had moderate, 6% reported severe and 6% recorded a severity of depressive symptoms, which placed them in the extremely severe category. Anxiety symptom levels were reported as mild by 10%, moderate in 23%, severe in 11% and extremely severe in 8.6% of respondents. Symptom levels in the stressed categories were reported as mild by 12%, moderate in 15%, severe in 13.3% and extremely severe in 4.8% of respondents.

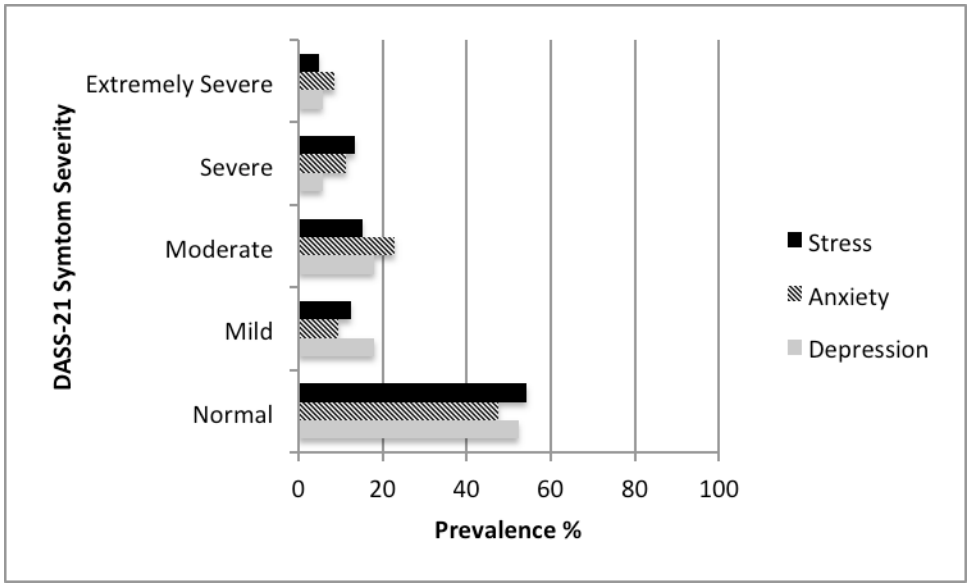


Figure 4.3 Prevalence and severity of symptoms relating to Depression (n =106), Anxiety (n =106) and Stress (n =106)

Questions relating to sleep patterns revealed that 91.4% of participants felt un-refreshed on waking, 73.3% were awoken by discomfort, 38.8% snored and 67.6% experienced difficulty getting to sleep. The mean (SD) composite score for sleep quality was 3.4 (1.3) with higher scores out of a possible 5 representing poorer sleep quality.

The current level of physical activity participation measured using the PAI revealed that 51.9% of the cohort were classed as sedentary, 28.3% had poor, 8.5% fair, 10.4% very good and 0.9% high participation, using the composite PAI score. Lifetime participation in sporting activities showed that 26.4% of participants had not participated in any sport continuously for a minimum of one season.

HRQoL was significantly reduced across all dimensions of the AQoL-6D, when compared to normative data (29) at a significance level of $p<0.05$ using the independent T-Test to compare means (Table 4.3). The total AQoL score, along with the individual dimensions of the instrument, were correlated with manifestations of JHS/EDS-HT (Systemic and Musculoskeletal), mental health findings, sleep quantity and quality and incontinence (Table 4.4). The three strongest correlations with the AQoL total scores were with fatigue (FSS individual scores), depression symptoms (DASS-21) and activity level (PAI composite score).

Table 4.3 Comparison of AQoL 6D study data to normative values (29)

	Current Study Mean values (SD) N= 106 Mean (SD)	Normative mean values (29) (SD) N= 2731	T- test P value 95%CI
AQoL 6D Total	0.61 (0.14)	0.84 (0.12)	<0.0001*
Independent Living	0.64 (0.22)	0.93 (0.13)	<0.0001*
Relationships	0.68 (0.19)	0.90 (0.13)	<0.0001*
Mental Health	0.59 (0.15)	0.75 (0.17)	<0.0001*
Coping	0.50 (0.17)	0.75 (0.18)	<0.0001*
Pain	0.41 (0.22)	0.86 (0.20)	<0.0001*
Senses	0.81 (0.19)	0.88 (0.11)	<0.0001*

Table 4.4 Correlations (Pearson's r) between the AQoL-6D total score and the 6 individual dimensional scores with manifestations of the JHS/EDS-HT.

	AQoL - Total Score	AQoL - Independent Living	AQoL - Relationship	AQoL -Mental Health	AQoL - Coping	AQoL - Pain	AQoL - Senses
Hakim 5 n = 106	**-0.270****	**-0.207****	-0.148	-0.202*	-0.212*	-0.232*	-0.239*
No. of joints affected by pain n = 106	**-0.474****	**-0.386****	**-0.339****	-0.237*	-0.207*	**-0.583****	**-0.437****
PAI Total Score n =106	**0.491****	**0.458****	**0.426****	**0.318****	**0.451****	**0.352****	0.140
Incontinence VAS n = 105	**-0.257****	-0.167	**-0.258****	-0.177	-0.127	-0.250*	**-0.264****
Cardiovascular Manifestations n = 105	**-0.368****	**-0.333****	**-0.348****	-0.212*	**-0.304****	-0.150	**-0.352****
Gastrointestinal features (number of features reported) n = 105	-0.143	-0.197*	-0.168	0.027	-0.018	-0.118	-0.140
Mean Individual FSS n =106	**-0.712****	**-0.629****	**-0.645****	**-0.422****	**-0.594****	**-0.556****	**-0.335****
Average hours sleep/night n = 103	0.028	-0.077	-0.173	0.174	-0.015	0.149	0.136
Sleep Quality (composite score) n = 103	-0.241*	-0.209*	-0.123	-0.189	-0.105	**-0.310****	-0.118
Depression – DASS-21 n =106	**-0.484****	**-0.255****	**-0.392****	**-0.691****	**-0.556***	-0.202*	-0.149
Anxiety – DASS-21 n =106	**-0.461****	**-0.328****	**-0.352****	**-0.382****	**-0.444****	**-0.305****	**-0.337****
Stress – DASS-21 n =106	**-0.297****	-0.061	-0.151	**-0.583****	**-0.373****	-0.175	-0.085

* Indicates $p \leq 0.05$, ** indicates $p \leq 0.005$

Prediction of QoL:

Stepwise multiple regression analysis was performed to assess the impact of manifestations of JHS/EDS-HT on the overall HRQoL of the cohort. The eight independent variables entered into the multiple regression analysis were: Self-perceived hypermobility (Musculoskeletal), number of joints affected by pain (Musculoskeletal), Dizziness (Systemic), Incontinence (Systemic), Gastrointestinal involvement (Systemic), physical activity level (Functional), Depression (Mental Health) and sleep duration, reflecting significant manifestations of the disorder. To enable a clearer interpretation of the influence of these variables on HRQoL, fatigue was not included in the analysis as it has previously been established as an influence on HRQoL (19). The multiple regression analysis retained three variables; DASS-21 Depression Score (Beta -0.412, $p < 0.001$), number of joints affected by pain (Beta -0.410, $p < 0.001$) and level of current physical activity (Beta 0.291, $p < 0.001$) (with the following regression equation accounting for 54.9% (Adjusted R^2 = 0.549, SE of the estimate = 0.093, F value 41.13 ($p < 0.0001$)) of the variance in the total AQoL-6D score:

AQoL-6D Total Score = 0.746 – (0.07 x DASS-21 Depression score) – (0.11 x no. of painful joints) + (0.002 x PAI Physical Activity)

With an inverse relationship between DASS-21 Depression scores and the number of joints affected by pain and the overall AQoL score, the regression equation shows that with increasing scores both on DASS-21 and for the number of joints affected, overall QoL decreases. Physical activity had a direct relationship with AQoL scores, with increasing participation in activity predictive of improved overall HRQoL.

Discussion:

This adult JHS/EDS-HT cohort reported a significantly lower health-related quality of life than that reported by a healthy population. Each dimension of the AQoL demonstrated significantly lower scores, revealing a global effect of the disease on HRQoL. The results of the current study indicated that, in addition to connective tissue features, systemic and mental health manifestations of the condition and level of physical activity have significant associations with HRQoL. This is the first study to identify potential predictors of HRQoL in an adult cohort affected by JHS/EDS-

HT, taking into account the overall profile of the disorder. Three potential predictors of HRQoL were identified, and these stand in addition to fatigue severity, which has previously been documented as a significant symptom of the disorder that can be predicted by aspects of AQoL-6D tool (19). Specifically, the extent of depressive symptoms as measured using the DASS-21, the total number of joints affected by pain and the current level of physical activity participation were predictive of overall HRQoL as reported by participants, thereby accounting for 54.9% of variance in the AQoL-6D total instrument scores.

The findings of this study support and extend those of previous research in JHS(18), EDS (involving all subtypes) (36) and EDS-HT (15) demonstrating significantly reduced HRQoL in individuals affected by the disorder compared to controls. Rombaut et al (2010) found, using the Rand 36-Item Health Survey tool, that participants with EDS-HT (N=32) had significantly lower HRQoL compared to controls in the domains of physical functioning, social functioning, limitations due to physical problems, limitations due to emotional problems, mental health, vitality, bodily pain, general health perception and physical component summary (15). Similarly, Albayrak et al (2015) found that individuals affected by Benign Joint Hypermobility Syndrome (a term they used synonymously with JHS) reported significantly reduced HRQoL using the Short Form 36 in the subscales of physical function, role physical, bodily pain, general health, role emotional and mental health. Additionally, these researchers found significantly higher depression scores, worse quality of sleep and greater fatigue when compared to matched controls (18), although the generalizability of their findings of this study is somewhat compromised by their exclusion criteria that limited the cohort studied to those least affected by the condition (18). The design of the current study, with a cohort size of 106 JHS/EDS-HT participants, including all levels of disease severity, allows for greater generalization of the results and increases the breadth of existing knowledge relating to the impact of the disorder on HRQoL.

Historically, health professionals have viewed JHS/EDS-HT as a condition that has minimal morbidity, primarily affecting the musculoskeletal system (37, 38). Only recently has the condition been recognized clinically as a multisystem disorder. It is therefore of particular interest that overall HRQOL in the current cohort could be

predicted by the severity of depressive symptoms and current physical activity participation, in addition to the number of joints affected by pain. Fatigue severity has already been identified as the most prevalent systemic symptom in this cohort, second only to polyarthralgia, and is strongly correlated with overall HRQoL.

Reduced physical activity has consistently been identified in paediatric (27, 39, 40) and adult (15, 41) populations affected by JHS/EDS-HT, for whom previous research has documented significantly lower sports participation (15), reduced mobility associated with muscle weakness (41), and reduced lower limb strength and endurance compared to unaffected individuals (42). Kinesiophobia, resulting in fear avoidance of movement, has been documented in JHS/EDS-HT and correlated with fatigue severity (35). Kinesiophobia has previously been identified as a possible mechanism for the progression from acute to chronic pain and is hypothesized to play a significant role in the progression to disability seen in JHS/EDS-HT (16, 43, 44), likely due to the resultant deconditioning as a result of reduced physical activity. The current study identified that while the majority of participants (73.8%) had taken part in at least 1 season of sport during their lifetime, at the time of the study the mean PAI total score placed the cohort in the "poor" category for physical activity. The evidence suggests that individuals affected by JHS/EDS-HT report reduced physical activity and likely have lower muscle strength and endurance compared to the general population, which provides the opportunity for clinicians to develop and test graded disease-appropriate exercise programs, and to implement strategies to manage kinesiophobia in order to address this aspect of the disorder.

Individuals affected by JHS/EDS-HT have previously been reported to have a higher incidence of anxiety, depression and use of anti-anxiety medication compared to the general public (11). The present study has shown that the overall HRQoL experienced by participants was moderately to strongly correlated with depression, anxiety and stress symptoms as measured using the DASS-21(45). These findings are consistent with a recent study that identified 74.8% of adult individuals diagnosed with EDS-HT scored high for anxiety symptoms while 22.4% scored high on depression symptoms (36). The overall psychological symptoms reported here are similar to those seen in patients seeking tertiary management of chronic pain (46). The possible reasons for the elevated reports of psychological comorbidities in this

population are likely to be multifactorial, including but not limited to; the delay in diagnosis/misdiagnosis of the disorder, poor professional recognition and understanding of JHS/EDS, the disparity between the experience of individuals with JHS and how health practitioners perceive the severity and impact of the disease on suffers (47), the experience of recurrent joint dislocations and injuries, chronic pain, elevated fatigue levels and the non-musculoskeletal features of the disorder (48). The results here provide further evidence that the psychological wellbeing of individuals affected by JHS/EDS-HT has a potentially significant impact on the overall burden of the disorder and warrants monitoring and management in those identified as being at risk of mental health manifestations.

Despite previous research demonstrating associations between urinary incontinence (adult (12) and paediatric populations (24)) and pelvic organ prolapse symptoms (21), with HRQoL, the current study identified only a weak association between increasing frequency of urinary incontinence ($p<0.005$) and overall quality of life. Only 7.7% of participants reported urinary incontinence or pelvic organ prolapse (UI/POP) (genitourinary features in Figure 4.1) and these features were not found to predict of the overall HRQoL in the multiple regression analysis. It has previously been identified that those affected by JHS/EDS-HT have an increased incidence of symptoms associated with UI/POP compared to the general population without necessarily causing the individuals significant concern (21). Their apparent lack of concern may result in affected individuals failing to seek professional assistance leading to a formal diagnosis of UI/POP, and highlights the need to include structured questionnaires in clinical practice relating to UI/POP symptoms to optimize management of the disorder.

As HRQoL is an indicator of the overall impact of a disorder on an individual, the identification of depressive symptoms, physical activity participation and number of joints affected by pain, in addition to fatigue severity as all being significant contributors to HRQoL, suggests that the development of management strategies targeting these factors is critical in any attempt to improve the lives of those affected by JHS/EDS-HT. Physical activity levels and psychological wellbeing have previously been identified as interconnected features in health related research, with both inactivity associated with poorer mental health and increased activity

participation associated with improvements in psychological conditions such as depression and anxiety (49). It has been established that physical activity, used as an intervention for depression, has a moderate affect on depression levels, and may be as effective as psychological and pharmacological interventions targeting depression (50). It is therefore probable that the reduced physical activity participation seen in JHS/EDS-HT plays a role in the development and/or maintenance of reduced psychological wellbeing. Accordingly, interventions aimed at increasing physical activity are likely to see a dual effect, improving both physical activity and depression symptoms.

No studies have as yet determined the efficacy of pain management strategies, involving cognitive behavioral therapy (CBT), implemented to address kinesiophobia, coping strategies and psychological manifestations, and graded physical activity participation to improve the HRQoL of adults with JHS/EDS-HT. CBT in a pain management setting has been shown to improve self-efficacy, depression and anxiety measures, reduce pain severity and catastrophising, and overall impact of the disorder on daily life, however HRQoL and fatigue levels were not incorporated into the objective measures of this study (51). Another study, which investigated the benefit of CBT and structured exercise programs, demonstrated that the intervention was successful in decreasing levels of kinesiophobia and increasing functional measures but did not employ psychological or direct measures of HRQoL (52) as outcome measures. However, a home based exercise programs have demonstrated significant improvements in the HRQoL of both children and adults with JHS/EDS-HT following completion of the intervention (53, 54). The use of incremental exercise programs utilizing exercise based quotas is a proven strategy to increase levels of physical activity in a graded and sustained manner in those affected by chronic pain (55). Although this method has not been specifically investigated in JHS/EDS-HT literature it seems likely that such an approach would be advantageous in increasing the activity levels of the JHS/EDS-HT population. It appears likely from the research currently available that a combination of a specific graded exercise program, and pain management strategies involving CBT would help to improve overall HRQoL, however, to confirm the efficacy of such a program in individuals with JHS/EDS-HT, further research is necessary. This would determine if management strategies

designed to manage pain, improve physical activity and address psychological manifestations in this population can indeed improve HRQoL.

The results of the current study suggest important avenues for further management of JHS/EDS-HT for both clinicians and researchers. The identification of significant systemic manifestations, such as severe fatigue and psychological symptoms in addition to musculoskeletal features of the disorder as contributing to overall HRQoL, emphasizes the importance of acknowledging the systemic nature of the disorder in the assessment and management of individuals diagnosed with JHS/EDS-HT. As anticipated, no single feature of the disorder adequately explained the variability in HRQoL as a result, it is unlikely that interventions aimed at a single aspect of the disorder would successfully improve HRQoL. This study provides a basis for advances in clinical practice, and should prompt research to determine the efficacy of management strategies combining psychological interventions, aimed at both pain management and psychological manifestations of the disorder, and physiotherapy, aimed at increasing physical activity participation, to jointly help reduce the impact of JHS/EDS-HT on the overall HRQoL of individuals affected by the disorder.

Disclosure statement:
The Author report no conflicts of interest.

See Appendix 8 for Strobe checklist for cross-sectional research.

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Chapter Five
Conclusion and Future Directions for Research

Synopsis of findings:

The results of the current study are in agreement with previously published literature in demonstrating the complex, multi-system nature of JHS/EDS-HT(9, 133, 134). In addition to the identification of a range of musculoskeletal manifestations of the condition, such as joint and muscle pain, history of dislocations and surgery for connective tissue features of the disorder, the current study has identified an array of systemic manifestations that are highly prevalent and associated with the overall quality of life experienced by those affected by the disorder.

A primary aim of this thesis was to investigate the prevalence, severity and impact of fatigue on individuals diagnosed with JHS/EDS-HT. The results indicate that fatigue is not only a frequently occurring manifestation of JHS/EDS-HT but it is strongly associated with reduced overall HRQoL. In the current sample of 117 adults with the condition, clinically significant fatigue was present in 79.5%, representing the most prevalent of all the non-musculoskeletal manifestations associated with the disorder. The levels of fatigue reported using the FSS scale (Appendix 3) indicate that its severity is comparable to that experienced in a range of systemic conditions, including MS, SLE and RA (102), where fatigue is a well-recognized manifestation of these disorders. The overall prevalence of significant fatigue found in this population mirrors previous results from studies in non-differentiated EDS cohorts, and from smaller JHS/EDS-HT-specific studies (8, 57, 59, 105). With the presence of fatigue previously identified as being associated with pain and aspects of quality of life (8, 60), and ranked as the most detrimental systemic manifestation in terms of QoL (9), the importance of identifying potential predicators was recognised. Five features of JHS/EDS-HT were found to predict the severity of fatigue in the current study cohort, accounting for 52.3% of the variance in the FSS mean score. Of the five potential predictors of fatigue severity, four were identified as being modifiable with appropriate investigation and intervention. The four modifiable predictors of fatigue severity were; orthostatic dizziness, participation in personal relationships and community, participation in physical activity, and satisfaction with the medical management and treatment options offered by health professionals. The successful identification of possible determinants of fatigue severity provides the opportunity for targeted investigation and management of individuals with JHS/EDS-HT. Fatigue

severity increased with the increased experience of orthostatic dizziness, the reduction in participation in physical activities and personal and community relationships, while dissatisfaction with the diagnostic process and subsequent management options increased fatigue severity.

HRQoL had previously been identified, in both non-differentiated EDS samples (60, 135) and in specific research relating to JHS/EDS-HT (86, 126), as being reduced compared to normative data. The evaluation and determination of potential predictors of overall HRQoL was therefore a primary aim of this thesis. HRQoL in the current cohort was significantly reduced across all domains measured using the AQoL – 6D tool (Appendix 4). The greatest differences between normative data and the results of the current cohort were seen in the domains of pain, independent living and aspects of coping. As fatigue was identified in the first study here as being predicted by the relationship domain of an individual's quality of life, it was excluded from the subsequent multiple regression analysis carried out to identify potential determinants of HRQoL. In the current cohort, it was identified that 55% of the variance in the overall HRQoL, as measured using the AQoL – 6D tool, was predicted by the amount and intensity of physical activity, the number of joints affected by pain, and the level of depression symptoms reported by participants. Overall HRQoL was reduced by decreased participation in physical activities, increasing symptoms relating to depression and increased numbers of joints affected by pain.

Current research studies explicitly investigating the mental health manifestations of JHS/EDS-HT (115, 120, 122) are limited. The results of the present research therefore provide much needed data specifically relating to the diagnosis of JHS/EDS-HT, characterising and defining the mental health manifestations of the disorder in this specific population. The mental health of individuals participating in the study was investigated using the DASS-21 (Appendix 5), a structured self-report tool indicating severity of symptoms relating to the clinical domains of depression, anxiety and stress, with questions regarding comorbid diagnoses and the mental health domain of the AQoL. The level of symptoms reported by participants in the study indicates that a large proportion of the cohort experience at least mild levels of symptoms relating to depression, anxiety and stress, with severe to extremely severe symptoms related to depression reported in 11%, anxiety in 21% and stress in 19%.

Although the DASS-21 is not designed to be used a diagnostic tool for depression, anxiety or stress, it is a good indicator of symptom severity in each of these mental health domains. The results of the current study therefore provide much needed confirmatory evidence that individuals with a diagnosis of JHS/EDS-HT experience symptoms indicative of reduced mental health.

Limitations of the studies:

The results of the present studies should be viewed within the limitations of their design. The study design was a cross-sectional analysis of individuals with JHS/EDS-HT, and, as a result, the information gathered represented the symptoms and manifestations that individuals were experiencing at one point in time (see Appendix 1 and 6). Further longitudinal research should be undertaken to provide disease progression data in this population. Structured questionnaires were utilized to ascertain the presence and severity of a range of symptoms and to quantify the current levels of HRQoL. Self-report questions were also utilized to identify the presence of other comorbid diagnoses or symptoms, which may have resulted in an under-reporting or bias towards reporting symptoms that participants felt were related to their JHS/EDS-HT diagnosis, or inaccurately reporting a previous diagnosis received by a medical professional (e.g. JHS or EDS-HT) or providing a "self" diagnosis. Attempts were made in the current study to minimize false reporting or reporting of "self" diagnoses by specifically asking participants to record diagnoses provided by a medical or health professional. In order to minimize the possibility of such bias in the future, structured questionnaires relating to symptoms such as autonomic dysfunction and specific questioning on manifestations would be of benefit. As the study aimed purely to investigate the disease presentation in JHS/EDS-HT, there was no control group that could provide comparative normative data when determining the significance of various findings. This limitation was overcome to an extent by the use of previously published normative and disease data for comparison in determining the significance fatigue and HRQoL results. Nevertheless, where normative data was not available for comparison, the results of the study can still be viewed as providing a representative description of the experienced manifestations of the disease process in the defined population.

The results of the Multiple Regression analysis in Study 1 and Study 2 should be viewed as being reflective of the study population. It should be noted that the prediction equation identified in each study may differ in an independent sample of individuals affected by JHS/EDS-HT. Future research is required to determine if the identified predictors in this study population are present in similar adult populations affected by JHS/EDS-HT and if improvements in Fatigue and or overall HRQoL are possible when addressing the identified predictors.

The study sample was recruited from support groups for connective tissue disorders (ConnecTed and EDSAUS) (see Appendix 2), and via word of mouth. The recruitment of individuals from support groups enabled specific recruitment of those affected by the condition, and given the absence of any clinics for adults with the condition, assisted in locating those who fulfilled the inclusion criteria for the study. There was the potential, however, for selection bias with those recruited from support groups potentially over-representing those who may be dissatisfied with their medical diagnosis and management. Those involved in support groups may be motivated toward searching for alternative answers and information to that provided by the medical community. There was a possibility of selection bias when considering which participants were able to partake in both the questionnaire and physical examination components of the research. Those who were able to attend the University of Sydney at the Lidcombe Campus were able to participate in the physical examination. It is possible those who were more significantly affected by their condition and those geographically isolated may not have been able to attend the physical examination component of the study. It should be noted the physical examination only provided supplementary data to that obtained via the questionnaires in Study One minimizing any potential for bias affecting the results of the study.

Implications for future research and clinical practice:

The results of the current studies have several of implications for future research and clinical practice in the area of JHS/EDS-HT. Adequate and timely diagnosis and management of individuals with a diagnosis of JHS/EDS-HT was a significant issue, and one requiring attention to improve the long-term outcome and disease morbidity in this population. In Sydney, while there is a well-known multidisciplinary clinic for

children with JHS/EDS-HT at the large tertiary hospital, The Children's Hospital at Westmead, this service is not available for those over 18 years of age. Many of these children are the first generation to receive a diagnosis, their affected parent/s having experienced the relatively encapsulated medical areas of rheumatology, dermatology, gastroenterology, neurology and ultimately psychiatry without definitive answers.

The proactive use of screening tools to identify and quantify the presence of a range of systemic manifestations of the disorder and the development of targeted treatment aimed at improving HRQoL and reducing fatigue severity would be likely to result in improved outcomes for patients with this disorder.

Improvement in the current diagnostic process:

While genetic markers have been identified for other EDS subtypes, there is currently no identified marker for the hypermobile subtype (136). The current process used in the diagnosis of JHS/EDS-HT remains a confusing, complex and subjective practice, with many individuals who seek professional input and diagnosis experiencing substantial diagnostic delays, multiple incorrect diagnoses given to explain their clinical presentation, and variable education and management for the disorder(62, 134). The diagnostic experience described by the current cohort of patients was not atypical for the disorder, with the mean delay in diagnosis following first onset of symptoms being reported as 20 years (N=53) and with 58% of individuals reporting dissatisfaction with the process and subsequent management of their disorder. Even more concerning is the previously reported estimation in 2008 that for every one individual diagnosed with JHS/EDS-HT, 19 remain undiagnosed and unmanaged for the disorder (134). The levels of dissatisfaction with diagnosis and management in the current cohort is not dissimilar to that reported in other chronic health conditions which rely on a diagnosis by exclusion, without definite objective clinical tests or procedures being available to confirm the presence of the condition, such as fibromyalgia (137) and CFS (138). The dissatisfaction with medical care in CFS was significantly associated with long delays in obtaining a diagnosis, inadequate explanation regarding the diagnosis and with being incorrectly provided with a psychiatric diagnosis for the condition (138). Similar associations were found in fibromyalgia, with those patients dissatisfied with their current medical treatment

being more likely to have waited significantly longer for a diagnosis, reported a greater number of symptoms related to the disorder, have functional impairment and a higher prevalence of chronic widespread pain compared to those who were satisfied with their management. These experiences documented in fibromyalgia and CFS mirror those reported by the current cohort of individuals affected by JHS/EDS-HT, highlighting the importance of improving the diagnostic process and management options provided to patients, with the aim of avoiding lengthy delays and unnecessary disease morbidity. The identification of factors contributing to the delay in diagnosis and management of individuals with JHS/EDS-HT is essential in order to address this issue.

The current diagnostic process for JHS/EDS-HT remains a clinical one based on the medical history and physical examination of those affected, following the exclusion of other HDCT. Despite the recognition that JHS and EDS-HT are likely the same phenotypic disorder (3, 134), the diagnostic process continues to rely on two separate criteria, the Villefranche Criteria for EDS-HT and the Brighton Criteria for JHS, and a single diagnostic title is yet to be established referring to the combined diagnosis. The diagnosis of JHS/EDS-HT largely relies on the presence of GJH, in addition to arthralgia and a range of connective tissue manifestations, however there is inconsistency when comparing the Villefranche and Brighton Criteria, with each utilising a different Beighton cut-off score to indicate the presence of GJH.

Globally, the accurate identification of GJH is also affected by a lack of international consensus on a specific definition for GJH, taking into account age, race, sex and even what constitutes normal range of motion in any given joint. Authors have previously recommended the need to develop a universally accepted definition for GJH together with standardised testing procedures and cut-off points to establish a diagnosis of GJH (10). The standardised Beighton Scoring protocol used in the studies that comprise this thesis is included as Appendix 4.

The recognition and variable clinical application of both the Beighton and the Brighton in evaluating individuals with symptomatic GJH is likely contributing to the variable success experienced by those seeking a diagnosis relating to symptomatic GJH. Explorative studies investigating the knowledge and clinical practice of

Rheumatologists (56, 71) and Physiotherapists (71, 139) have identified inconsistent use of the Beighton score to establish and diagnosis of GJH, little recognition of the systemic nature of the JHS/EDS-HT, and variable use of the Brighton screening tool, when attempting to establish a diagnosis for the condition. The lack of clinical knowledge relating to both GJH and JHS/EDS-HT, together with the assessment tools currently available, is likely contributing significantly to difficulties experienced by individuals affected when attempting to obtain a diagnosis. Literature reports only 32% of UK physiotherapists receive formal education relating to JHS (139) while a survey of USA physical therapists revealed that 39% were unaware of the existence of the condition (71). There is a clear need for increased education during the training phase of health and medical professionals who, in a primary care capacity, are likely to encounter undiagnosed individuals with symptoms relating to a connective tissue disorder such as JHS/EDS-HT. Such education will help to ensure there is early identification, diagnosis and appropriate referral of those affected by the condition.

While there are objective tests available for several of the signs and symptoms of JHS/EDS-HT such as Postural Orthostatic Tachycardia Syndrome, orthostatic hypotension, generalised hyperalgesia, gastric transit times, hernias, varicosities and prolapses, the lack of specific molecular tests of the condition leaves the diagnostic process reliant on clinical reasoning and the exclusion of other HDCTs. This is likely to contribute to the delay in diagnosis and implementation of appropriate interventions, and the development of subsequent psychosocial manifestations. Several authors have recommended further investigation into the molecular basis of JHS/EDS-HT, to identify the causal gene/s responsible for the expression of the disorder (64, 134, 136). Due to the heterogeneous nature of JHS/EDS-HT it has been hypothesised that instead of one gene accounting for the diagnosis, there may be a number of different underlying molecular subtypes accounting for the clinical presentation seen in those with a current diagnosis of JHS/EDS-HT (136, 140). Regardless of the number of underlying causal genes identified in the future, the development of a molecular diagnosis relating to JHS/EDS-HT would be pivotal to improving the accuracy and certainty relating to the diagnostic process.

Key recommendations arising from the current thesis are; firstly, the establishment of concise objective diagnostic criteria to establish a diagnosis of JHS/EDS-HT, enabled

by the development of a single diagnostic label for the disorder, and secondly, that future research should aim to establish a molecular diagnosis for the disorder.

Screening for systemic manifestations and overall quality of life:

The complex heterogeneous presentation of JHS/EDS-HT poses a significant challenge to health and medical practitioners in providing holistic care addressing the manifestations of the condition that are not always superficially apparent or recognized as impacting on the individuals over all QoL. The significant contribution of systemic manifestations, such as the presence of severe fatigue, gastrointestinal, genitourinary, cardiovascular and psychological symptoms, in determining the overall morbidity associated with the condition has been documented in previous research, highlighting the need for the identification and management of these features (9, 55, 57). An important finding of the current research was the identification of severe fatigue as a highly prevalent manifestation and the most significant systemic feature affecting the overall HRQoL in the study population. This finding echoed the results of previous studies identifying fatigue as a manifestation that has the potential to have a significant impact on the individual. In addition to fatigue severity, specific screening tools were used to establish symptom severity in mental health domains (DASS-21) and overall HRQoL in the current study, both of which indicated that the defined population experience greater levels of symptoms related to psychological distress and worse overall quality of life compared to those not affected by the disorder. The current study supports the conclusion of previous research, which identified the importance of evaluating the presence of systemic features of JHS/EDS-HT needed to improve the assessment and management of patients with this condition (55, 133, 141).

Without specific questioning relating to the systemic features associated with JHS/EDS-HT, these manifestations may go unreported and unmanaged in many individuals. An example of one such systemic feature is orthostatic dizziness, where patients experience dizziness on rising from recumbent positions, after exercise, or after a hot shower. If they are sedentary due to pain, fatigue and low levels of physical activity, health professionals may attribute the symptom to deconditioning. The connection between the patient's joint hypermobility, hyperextensible skin, abnormal scarring, gastric upset, uterine prolapse and hernia in childhood is not made.

Consequently, there is a need to screen and manage systemic features of the condition proactively and early in a multidisciplinary manner, potentially reducing the morbidity associated with these manifestations. Features not directly related to the connective tissue manifestations are not evaluated during the diagnosis of the JHS/EDS-HT, using either the Villefranche or the Brighton criteria. Specific attention needs to be placed on incorporating these features, such as fatigue and mental health features of the disorder, into the assessment, diagnosis and management of the condition. A fundamental recommendation of the current study is the inclusion of specific, short, reliable and valid screening tools following initial diagnosis and during the follow-up consultations, to provide valuable information on the systemic features of the disorder that require further investigation and management in individuals with JHS/EDS-HT. This recommendation supports previous literature advocating the use of appropriate questioning relating to significant systemic features in the assessment of multi-system manifestation and HRQoL. Such questioning offers the potential to monitor the effectiveness of intervention strategies and modify treatments as required (141).

Management of fatigue and HRQoL in JHS/EDS-HT:

The holistic management of individuals with JHS/EDS-HT likely lies in the development of multidisciplinary interventional programs incorporating strategies to address both musculoskeletal and functional impairments experienced by individuals, while extending to include strategies to address the myriad of significant non-musculoskeletal features associated with the disorder. With the identification of a set of predictors that can determine the severity of fatigue, the most prevalent of systemic features, and overall HRQoL of individuals affected by the condition, there can be a new focus on the interventions that are likely to directly improve these important aspects of an individual's lived experience. Given the wide range of factors that potentially influence an individual's overall fatigue severity and overall HRQoL, the results of study one allow the development of a targeted multidisciplinary approach to the management of individuals with JHS/EDS-HT.

There have been strong recommendations for the development of multidisciplinary approach to the management of the individuals affected by JHS/EDS-HT (9, 57, 64). With limited studies investigating the management of JHS/EDS-HT and the specific

use of multidisciplinary teams, the identification of aspects of the condition that contribute to fatigue severity and the overall HRQoL experienced by individuals affected by the disorder opens the door for substantial improvements in the current evidence-based management strategies in this population. Current management strategies utilising a multidisciplinary team approach have predominately focused on functional and pain related measures to determine the effectiveness of strategies (129, 130, 132). HRQoL measures have been utilized by a number of studies in the evaluation of the overall effect of the management strategies (129), however fatigue severity has not featured as a specific outcome measure in previous research.

Based on the results of the current research, the inclusion of management strategies to address levels of physical activity participation, coping strategies to improve participation in community and family interactions, pain management, psychological intervention, investigation and management of orthostatic intolerance and education regarding the disorder and potential management strategies, may help to reduce both fatigue severity and improve overall HRQoL. To evaluate the efficacy of intervention strategies targeting overall HRQoL and fatigue severity, measures specifically assessing both these features should be utilized as outcome measures in future research.

One important consideration in the development of management strategies for JHS/EDS-HT is the high reported levels of patient dissatisfaction with their medical management. Previous research has identified that when a patient is actively involved in the management and decision making process and is allowed to ask questions related to their diagnosis, there are greater levels of psychological well-being (142), increased satisfaction with their healthcare provider, and a greater sense of control over their illness (143). Given the multi-system nature of JHS/EDS-HT and the potential number of management strategies that could be implemented to address all manifestations of the disorder, careful consideration should be paid to the likely compliance and ability of an individual to address all features of the condition. The management of an individual with JHS/EDS-HT would be best managed with a single physician who is responsible for coordinating multi-disiplinary care for the individual affect by JHS/EDS-HT. Attention should be paid to the importance of patient education and “choice” in determining which treatment options are implemented in

the management of their condition. There is likely efficacy in addressing individual contributors to fatigue severity and overall HRQoL, rather than taking an all or nothing approach to the condition, and possibly a realistic management approach in JHS/EDS-HT. Such an approach has proven effective in the secondary reduction of cardiac risk following a cardiac event compared to conventional care, with patients who made an educated choice as to which cardiac risk factor they wished to specifically address showing greater improvements not only in the individual risk factors but also across the global coronary risk profile (144). Such a finding indicates that patient centered-care with guided self-determination of treatment choices may be a beneficial management strategy in conditions such as JHS/EDS-HT, where the disorder is associated with numerous disease manifestations and potential management options. Further specific research into the efficacy of such an intervention in JHS/EDS-HT is necessary to determine if this approach could not only improve specific patient outcomes related to disease manifestations and HRQoL, but also improve patient satisfaction with their disease management.

Conclusion:

This thesis provides a detailed description of the type and range of manifestations associated with a diagnosis of JHS/EDS-HT. The identification of fatigue severity as a significant non-musculoskeletal manifestation of the disorder, and the subsequent determination of the potential predictors of both fatigue severity and the overall HRQoL, provide new information that is likely to progress the management of the disorder. The findings confirm that JHS/EDS-HT is not only a multisystem condition but a complex systemic disorder that has the potential to result in significant disease morbidity, functional impairment and disability. The results of this thesis provide promising direction for future research, to assess the efficacy of management strategies addressing the identified predictors of fatigue severity and HRQoL, with the aim of improving the life experience of those affected by JHS/EDS-HT.

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Appendices

Appendix 1: Participant information statement JHS/EDS-HT and GJH Study

THE UNIVERSITY OF SYDNEY

Sydney Medical School
Discipline of Biomedical Science

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A normative study of Generalised Joint Hypermobility Syndrome.

PARTICIPANT INFORMATION STATEMENT

(1 What is the study about?

Many children, adolescents and adults are hypermobile (have loose or double joints). We think they have more musculoskeletal pain and fatigue and are at higher risk of sports injury than people who are not hypermobile. Because joint hypermobility is sometimes accompanied by widely varying symptoms and signs - including joint pains, joint instability, brittle bones, lax joints, fragile stretchy skin, tendency to bruise, hernias and prolapse and poor balance, some of these people will have seen medical and allied health professionals and have been undiagnosed. We aim to look at the prevalence of the broad range of signs and symptoms in an adult population of individuals who perceive themselves to be hypermobile.

(2 Who is carrying out the study?

A/Prof Leslie Nicholson	Associate Professor, Discipline of Biomedical Sciences, Sydney medical School, The University of Sydney	Ph: 02 9351 9369
Dr Louise Tofts	Staff Specialist, Paediatric Rehabilitation Medicine	Ph. 02 9845 2132
Miss Verity Pacey	Senior Physiotherapist and PhD candidate Childrens' Hospital Westmead	Ph. 02 9845 3369
Dr Bronwen Ackermann	Senior Lecturer, Discipline of Biomedical Sciences, Sydney Medical School, The University of Sydney	Ph. 02 9519 4084
Ms Anne Krahe	Orange Health Services Orange	Ph. 04xx xxx xxx

(3 What does the study involve?

We will ask you to complete a questionnaire that will include information related to your age, gender, ethnicity and activity level. You will also be asked about joint and soft tissue soreness, joint instability episodes, family history of joint hypermobility, fatigue, fainting episodes, stress incontinence, gastrointestinal symptoms and history of low trauma fractures.

We will record your height and weight; screen for joint hypermobility using the Beighton score (tests the joint range in your thumbs, little fingers, elbows, knees and spine). Then we will check your skin for elasticity and assess the thickness of your skin using diagnostic ultrasound, test for hypermobility in your hips, knees and ankles, assess your foot posture in standing and test your shoulder, wrist and knee joint laxity. We will ask you to perform a balance test on single leg stance on both legs.

If you are currently experiencing any joint or muscle pain, please inform the assessor as we will omit the tests relevant to these areas. If you have widespread joint/muscle pain we may exclude you from participation and suggest you seek a medical opinion. Please let the assessor know if you have experienced any episodes of knee-cap or shoulder dislocation.

All testing will be performed at the Faculty of Health Sciences (Lidcombe), Narrabeen Sports Medicine Centre or at your home at a time that suits you. No testing will cause you any pain. You will be informed of your personal results at the time of testing.

(4 How much time will the study take?

Completing the questionnaires and testing should take 45 minutes to 1 hour of your time, on one occasion only.

(5 Can I withdraw from thestudy?

Being in this study is completely voluntary - you are not under any obligation to consent and - if you do consent - you can withdraw at any time without affecting your relationship with The University of Sydney, or the Narrabeen Sports Medicine Centre..

(6 Will anyone else know the results?

All aspects of the study, including results, will be strictly confidential and only the researchers will have access to information on participants
A report of the study may be submitted for publication, but individual participants will not be identifiable in such a report.

(7 Will the study benefit me?

We cannot and do not guarantee or promise that you will receive any benefits from the study. If we identify problems you have which would get better with treatment we will refer you for appropriate treatment. We hope the results from the study will allow us to understand your condition better and be able to provide the medical and allied health professions with better diagnostic information. This information will also allow us to plan future studies of treatments for this condition.

(8 Can I tell other people about the study?

You are welcome to direct others to our posters if they are interested in participating in this study.

(9 What if I require further information about the study or my involvement in it?

When you have read this information, Dr Nicholson will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact any of the researchers (see point 2 on the previous page)

(10 What if I have a complaint or any concerns?

Any person with concerns or complaints about the conduct of a research study can contact The Manager, Human Ethics Administration, University of Sydney on +61 2 8627 8176 (Telephone); +61 2 8627 8177 (Facsimile) or ro.humanethics@sydney.edu.au (Email).

This information sheet is for you to keep

Appendix 2: Online introduction for JHS/EDS-HT Study:

At the University of Sydney we are undertaking 2 streams of research into heritable disorders of connective tissue. One stream is paediatric in collaboration with the Children's Hospital at Westmead and the other is an adult stream. As physiotherapists and rehab physicians we are particularly interested in the effects of joint hypermobility on health and wellbeing.
We are currently recruiting people between the ages of 16 and 75 who have joint hypermobility for a study to look at the systemic and musculoskeletal signs and symptoms and how these affect quality of life. If you have been diagnosed with Joint Hypermobility Syndrome or Ehlers-Danlos Syndrome (Type III or hypermobility type) you may qualify for the study.
The study is being conducted at the Faculty of Health Science in Lidcombe (Sydney). Participation would involve completing some questionnaires (we can send them to you electronically so you can complete them at your leisure) and an assessment of your joint and soft tissue hypermobility (should take about 1 hour).
Understanding hypermobility and getting the research "out-there" to medical and allied health professionals is an important step in improving the lives of people with these diseases.
Even if you cant get to Sydney but would like to participate, you can complete the questionnaire portion of the study. If you would like more information regarding this study or you would like to participate, please contact:

Anne Krahe – akra2983@uni.sydney.edu.au OR ph. 04xx xxx xxx

Appendix 3 Fatigue Severity Scale

FSS Questionnaire							
During the past week, I have found that:	**Score**						
1. My motivation is lower when I am fatigued.	1	2	3	4	5	6	7
2. Exercise brings on my fatigue.	1	2	3	4	5	6	7
3. I am easily fatigued.	1	2	3	4	5	6	7
4. Fatigue interferes with my physical functioning.	1	2	3	4	5	6	7
5. Fatigue causes frequent problems for me.	1	2	3	4	5	6	7
6. My fatigue prevents sustained physical functioning.	1	2	3	4	5	6	7
7. Fatigue interferes with carrying out certain duties and responsibilities.	1	2	3	4	5	6	7
8. Fatigue is among my three most disabling symptoms.	1	2	3	4	5	6	7
9. Fatigue interferes with my work, family, or social life.	1	2	3	4	5	6	7

Appendix 4 AQoL-6D

AQoL-6D (Data Collection Copy Simplified)

Tick the box that best describes your situation as it has been over the past week

Q1 How much help do you need with jobs around your place of residence (eg preparing food, cleaning, gardening)?

- ❑ I can do all these tasks very quickly and efficiently without any help
- ❑ I can do these tasks relatively easily without help
- ❑ I can do these tasks only very slowly without help
- ❑ I cannot do most of these tasks unless I have help
- ❑ I can do none of these tasks by myself.

Q2 How easy or difficult is it for you to get around by yourself outside your place of residence (eg to go shopping, visiting)?

- ❑ getting around is enjoyable and easy
- ❑ I have no difficulty getting around outside my place of residence
- ❑ I have a little difficulty
- ❑ I have moderate difficulty
- ❑ I have a lot of difficulty
- ❑ I cannot get around unless somebody is there to help me.

Q3 How easy or difficult is it for you to move around (using any aids or equipment you need eg a wheelchair, frame or stick)?

- ❑ I am very mobile
- ❑ I have no difficulty with mobility
- ❑ I have some difficulty with mobility (for example, going uphill)
- ❑ I have difficulty with mobility. I can go short distances only.
- ❑ I have a lot of difficulty with mobility. I need someone to help me.
- ❑ I am bedridden.

Q4 How difficult is it for you to wash, toilet, dress yourself, eat or care for your appearance?

- ❑ these tasks are very easy for me
- ❑ I have no real difficulty in carrying out these tasks
- ❑ I find some of these tasks difficult, but I manage to do them on my own
- ❑ many of these tasks are difficult, and I need help to do them
- ❑ I cannot do these tasks by myself at all.

Q5 How happy are you with your close and intimate relationships?

- ❑ very happy
- ❑ generally happy
- ❑ neither happy nor unhappy
- ❑ generally unhappy
- ❑ very unhappy

Q6 Does your health affect your relationship with your family?

- ❑ my role in the family is unaffected by my health
- ❑ there are some parts of my family role I cannot carry out
- ❑ there are many parts of my family role I cannot carry out
- ❑ I cannot carry out any part of my family role.

Tick the box that best describes your situation as it has been over the past week

Q7 Does your health affect your role in your community (eg residential, sporting, church or cultural groups)?

- ❑ my role in the community is unaffected by my health
- ❑ there are some parts of my community role I cannot carry out
- ❑ there are many parts of my community role I cannot carry out
- ❑ I cannot carry out any part of my community role.

Q8 How often did you feel in despair over the last seven days?

- ❑ never
- ❑ occasionally
- ❑ sometimes
- ❑ often
- ❑ all the time.

Q9 How often did you feel worried in the last seven days?

- ❑ never
- ❑ occasionally
- ❑ sometimes
- ❑ often
- ❑ all the time.

Q10 How often do you feel sad?

- ❑ never
- ❑ rarely
- ❑ some of the time
- ❑ usually
- ❑ nearly all the time.

Q11 Do you normally feel calm and tranquil or agitated?
I am

- ❑ always calm and tranquil
- ❑ usually calm and tranquil
- ❑ sometimes calm and tranquil, sometimes agitated
- ❑ usually agitated
- ❑ always agitated.

Q12 How much energy do you have to do the things you want to do?
I am

- ❑ always full of energy
- ❑ usually full of energy
- ❑ occasionally energetic
- ❑ usually tired and lacking energy
- ❑ always tired and lacking energy.

Q13 How often do you feel in control of your life?

- ❑ always
- ❑ mostly
- ❑ sometimes
- ❑ only occasionally
- ❑ never.

Tick the box that best describes your situation as it has been over the past week

Q14 How much do you feel you can cope with life's problems?

- ❑ completely
- ❑ mostly
- ❑ partly
- ❑ very little
- ❑ not at all.

Q15 How often do you experience serious pain?

I experience it

- ❑ very rarely
- ❑ less than once a week
- ❑ three to four times a week
- ❑ most of the time.

Q16 How much pain or discomfort do you experience?

- ❑ none at all
- ❑ I have moderate pain
- ❑ I suffer from severe pain
- ❑ I suffer unbearable pain.

Q17 How often does pain interfere with your usual activities?

- ❑ never
- ❑ rarely
- ❑ sometimes
- ❑ often
- ❑ always

Q18 How well can you see (using your glasses or contact lenses if needed)?

- ❑ I have excellent sight
- ❑ I see normally
- ❑ I have some difficulty focusing on things, or I do not see them sharply. *E.g. small print, a newspaper or seeing objects in the distance.*
- ❑ I have a lot of difficulty seeing things. *My vision is blurred. I can see just enough to get by with.*
- ❑ I only see general shapes. *I need a guide to move around*
- ❑ I am completely blind.

Q19 How well can you hear (using your hearing aid if needed)?

- ❑ I have excellent hearing
- ❑ I hear normally
- ❑ I have some difficulty hearing or I do not hear clearly. *I have trouble hearing softly-spoken people or when there is background noise.*
- ❑ I have difficulty hearing things clearly. *Often I do not understand what is said. I usually do not take part in conversations because I cannot hear what is said.*
- ❑ I hear very little indeed. *I cannot fully understand loud voices speaking directly to me.*
- ❑ I am completely deaf.

Tick the box that best describes your situation as it has been over the past week

Q20 How well do you communicate with others (talking, signing, texting, being understood by others and understanding them)?

- ❑ I have no trouble speaking to them or understanding what they are saying
- ❑ I have some difficulty being understood by people who do not know me. I have no trouble understanding what others are saying to me.
- ❑ I am understood only by people who know me well. I have great trouble understanding what others are saying to me.
- ❑ I cannot adequately communicate with others.

Appendix 5 DASS-21

DASS21

Name: *Date:*

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found it hard to wind down	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5	I found it difficult to work up the initiative to do things	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I experienced trembling (eg, in the hands)	0	1	2	3
8	I felt that I was using a lot of nervous energy	0	1	2	3
9	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting agitated	0	1	2	3
12	I found it difficult to relax	0	1	2	3
13	I felt down-hearted and blue	0	1	2	3
14	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15	I felt I was close to panic	0	1	2	3
16	I was unable to become enthusiastic about anything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life was meaningless	0	1	2	3

Appendix 6 Standardised Beighton Scoring Protocol

THE UNIVERSITY OF SYDNEY

Physical Data Collection Protocol: JHS/EDS-HT Study

Anne Krahe
Associate Professor Leslie Nicholson
Dr Bronwen Ackermann

1

1. Beighton Score (Beighton, Solomon, & Soskolne, 1973)

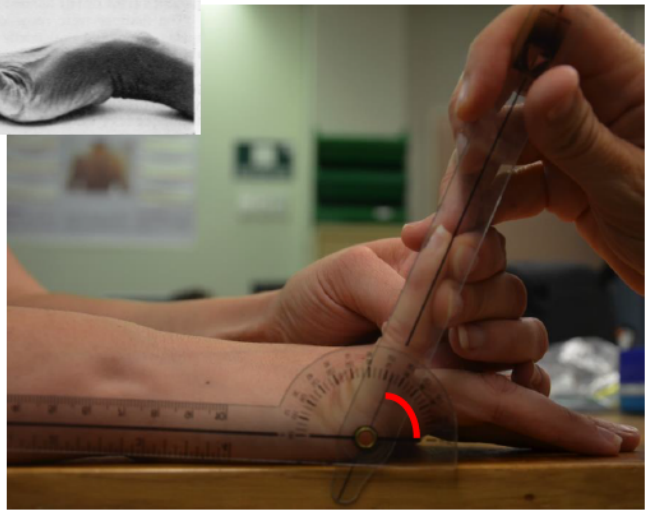
a. Passive hyperextension of the fifth metacarpophalangeal joint (MCP) – score one for each side, max score of 2:

THIS TEST HAS THE LOWEST INTER-RATER RELIABILITY OF ALL THE COMPONENTS OF THE BEIGHTON SCORE.

Inter-rater Reliability †	Kappa	99% Confidence Interval
Right 5th digit	0.61	0.15, 1.07
Left 5th digit	0.40	-0.01, 0.81

Test Position:	Motion Tested:	Positioning Goniometer:	Score:
Sitting on chair elbow flexed & forearm resting in pronation on the table.	Patient Passively hyperextends the 5th MCP joint as far as comfortably possible	Medial aspect of the 5th MCP joint, in line with the 5th proximal phalanx and metacarpal.	1= ≥90° MCP hyperextension 0= <90° MCP

Original descriptor – "Passive dorsiflexion of the little fingers beyond 90°"



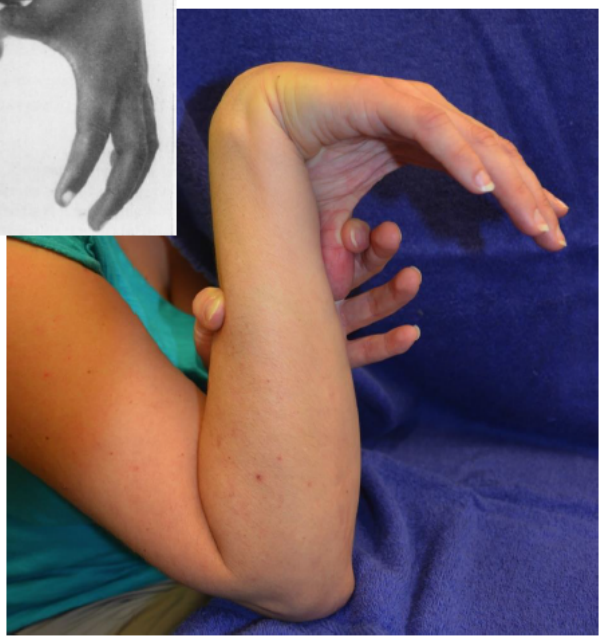
†Juul-Kristensen, B., Røgind, H., Jensen, D. V., & Remvig, L. (2007). Inter-examiner reproducibility of tests and criteria for generalized joint hypermobility and benign joint hypermobility syndrome. *Rheumatology, 46*(12), 1835-1841.

b. Passive Opposition of thumb to flexor side of forearm – score 1 for each side, max score of 2:

Inter-rater Reliability †	Kappa	99% Confidence Interval
Right 1st digit	1.00	1.00, 1.00
Left 1st digit	0.94	0.79, 1.09

Test Position:	Motion Tested:	Positioning Goniometer:	Score:
Sitting– elbow flexed and forearm in mid position. Wristed flexed.	Passive hyperflexion of the 1st digit to the anterior surface of the Radial side of the forearm	No goniometer	1= Tip or more of the 1st digit approximates the forearm 0= The thumb does not approximate the forearm at all

Original descriptor – "Passive apposition of the thumbs to the flexor aspects



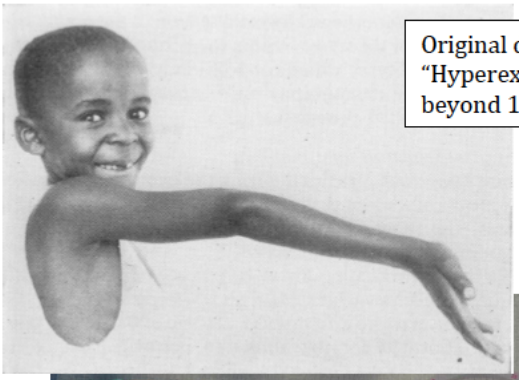
†Juul-Kristensen, B., Røgind, H., Jensen, D. V., & Remvig, L. (2007). Inter-examiner reproducibility of tests and criteria for generalized joint hypermobility and benign joint hypermobility syndrome. *Rheumatology*, *46*(12), 1835-1841.

c. Passive hyperextension of the elbow joint – score 1 for each side, max score of 2:

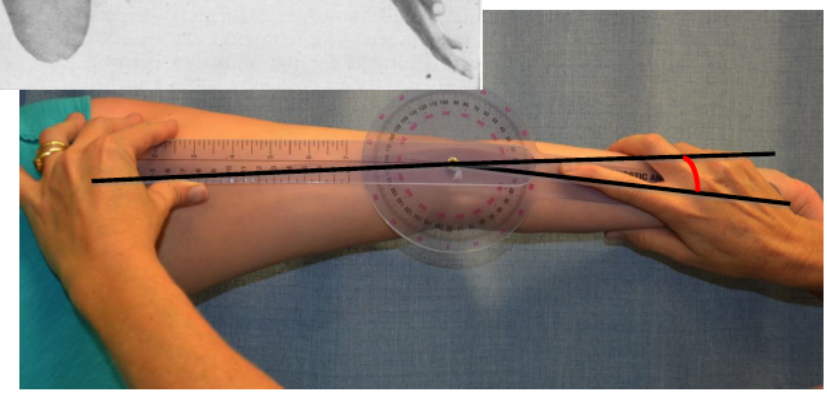
THIS TEST HAS THE SECOND LOWEST INTER-RATER RELIABILITY OF ALL THE COMPONENTS OF THE BEIGHTON SCORE.

Inter-rater Reliability †	Kappa	99% Confidence Interval
Right elbow	0.64	0.28, 1.00
Left elbow	0.34	-0.10, 0.78

Test Position	Motion tested	Positioning of goniometer	Score
Subject standing shoulders abducted to 90° forearm supinated, subject extends elbow joint and examiner provides a gentle overpressure while measuring.	Passive extension of the elbow	Goniometer placed over the lateral elbow joint in line with the humerus and the radial styloid	1= ≥10° of hyperextension 0 = < 10° of hyperextension



Original descriptor – "Hyperextension of the elbows beyond 10°."

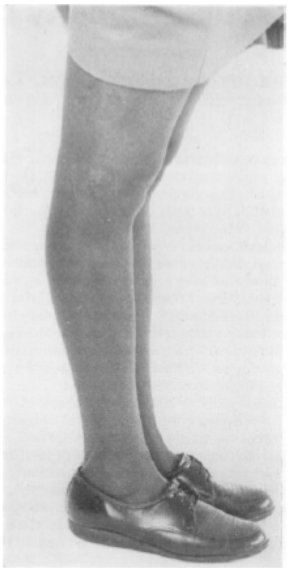


†Juul-Kristensen, B., Røgind, H., Jensen, D. V., & Remvig, L. (2007). Inter-examiner reproducibility of tests and criteria for generalized joint hypermobility and benign joint hypermobility syndrome. *Rheumatology*, *46*(12), 1835-1841.

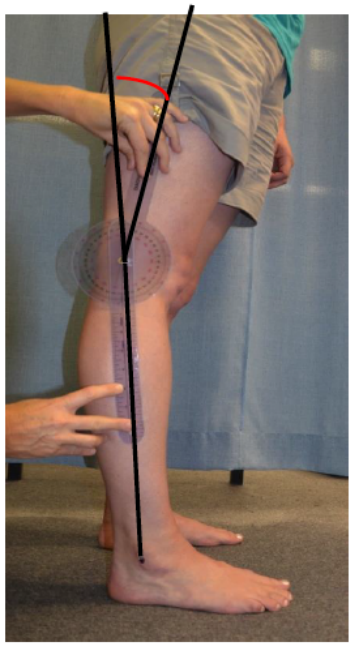
d. Passive hyperextension of the knee joint – score 1 for each side, max score of 2:

Inter-rater Reliability †	Kappa	99% Confidence Interval
Right knee	0.90	0.72, 1.08
Left knee	0.85	0.64, 1.06

Test Position	Motion Tested	Positioning of Goniometer	Score
Subject standing, and is asked to "lock out their knee"	Knee Hyperextension	Placed on the lateral aspect of the leg over the tibiofemoral joint, in line with the greater trochanter and lateral malleolus.	1= ≥ 10° hyperextension 0= < 10° hyperextension



Original descriptor – "Hyperextension of the knees beyond 10°."

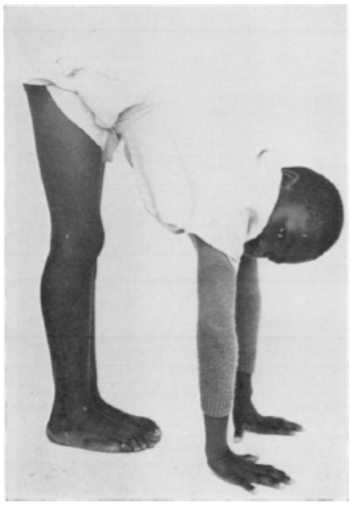


†Juul-Kristensen, B., Røgind, H., Jensen, D. V., & Remvig, L. (2007). Inter-examiner reproducibility of tests and criteria for generalized joint hypermobility and benign joint hypermobility syndrome. *Rheumatology*, *46*(12), 1835-1841.

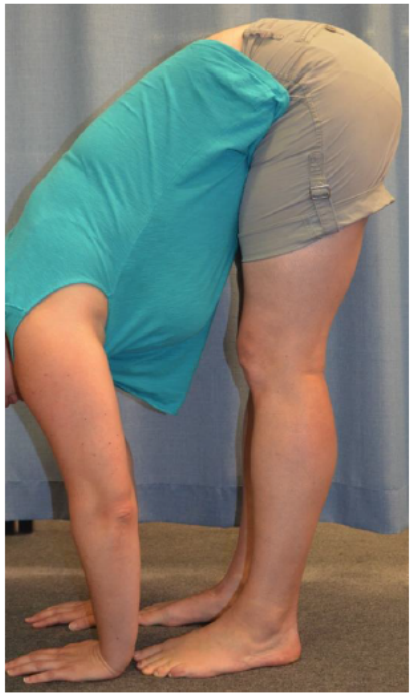
e. Forward flexion of the trunk (feet shoulder width apart) – max score of 1:

Inter-rater Reliability †	Kappa	99% Confidence Interval
Trunk Forward Flexion 0.88 (0.67, 1.09)	0.88	0.67, 1.09

Test Position	Motion Tested	Positioning of Goniometer	Score
Subject standing barefoot, with feet shoulder width apart	Hip and spinal hyperflexion	No goniomenter	1= able to place whole palms on the floor immediately in front of their feet 0= Unable



Original descriptor – "Forward flexion of the trunk, with knees straight, so that the palms of the hands rested easily on the floor."



Total maximum score = 9

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2. Weight:
   The subject is weighed in bare feet with minimal clothing.
   Weight is recorded in kg.

3. Height:
   The subject's height is measured, without shoes
   Recorded in cm.

4. BMI:
   Calculated as weight in kg / height in metres^2

Appendix 7: Variable collected in questionnaire and physical examination for Study 1 and 2 (* = Study 1 only)

Variables collected in questionnaire and physical examination (*) for Study 1 and 2
Sex
Age
JHS/ EDS – HT Diagnosis
Family history hypermobility
Diagnosis of EDS/OI/ Marfan/other connective tissue disorder
Hakim 5
Number of joints affected by pain attributed to GJH on body chart
Soft tissue pain noted on body chart
History of joint dislocation - listed joints
Fracture history
Sporting history
Ease of bruising measured on VAS
Incontinence measured on VAS
Dizziness measured on VAS
Stool Frequency
History of hernia
Fatigue Severity Score (FSS)
Satisfaction with diagnosis and management related to diagnosis relating to GJH
Previous surgery for Connective tissue features of the disorder
Physical activity index
Sleep related questions
Previous medical diagnosis
DASS- 21 questionnaire
AQOL_6D questionnaire
Beighton Score *
Weight KG *
Height m *
BMI *
Marfanoid Habitus *
Skin Signs *
Eye signs *
Duration Symptoms prior to diagnosis

Appendix 8: STROBE Checklist for study 2

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Relevant section and Page No. in manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	See abstract and study title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	See abstract page
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Refer to introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Refer to the last paragraph of the introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Refer to first paragraph of introduction
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Refer to first paragraph of introduction
Participants	6	(*a*) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Refer to first paragraph of the introduction
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Refer to the metholdology section of the paper
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Refer to the methodology section of the paper and relevant references
Bias	9	Describe any efforts to address potential sources of bias	Refer to limitation section of the conclusion of the thesis.
Study size	10	Explain how the study size was arrived at	Refer to Figure 1.1

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Refer to the methodology
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	See statistical analysis section of methodology
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	See Figure 1.1 in results section.
		(b) Give reasons for non-participation at each stage	As above
		(c) Consider use of a flow diagram	As above
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	See results section first paragraph
		(b) Indicate number of participants with missing data for each variable of interest	See results section
Outcome data	15*	*Cross-sectional study*—Report numbers of outcome events or summary measures	See results section and relevant tables.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N/A
		(*b*) Report category boundaries when continuous variables were categorized	See methodology and results
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	See methodology and result section of paper
Discussion			
Key results	18	Summarise key results with reference to study objectives	See first paragraph of the discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	See limitation section of conclusion chapter of thesis
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	See discussion section of paper
Generalisability	21	Discuss the generalisability (external validity) of the study results	See discussion section of the paper
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	See disclosure statement

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/).