Generalized Joint Hypermobility (GJH) and anxiety, the impact on daily functioning, societal and sport participation in adolescents and young adults

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Generalized Joint Hypermobility (GJH) and anxiety, the impact on daily functioning, societal and sport participation in adolescents and young adults

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Chapter 1

General introduction

Anne, a motivated 17-years-old girl, just graduated high school and will start her professional dance education at the Academy of Theatre and Dance at the Amsterdam University of the Arts (ATD). She is highly committed to everything she does and although her family and friends expect her to excel within her professional dance career, Anne herself feels a bit tense towards the start at the ATD. She has danced her whole life in her local dance company and experiences the performance of splits and high kicks as easy as any other dance movement. Her dance teacher says she is talented, thin and has the gift of being hypermobile. Although she "dances trough life" she has pain complaints in her joints and soft tissues sometimes, especially after overloading. During the mandatory medical screening by the ATD, Anne was told that she had generalized joint hypermobility and was explained this could also be temporarily as part of her pubertal growth. Anne feels she benefits from her joint hypermobility as do her parents. She excels within dance and experiences besides the occasional pain complaints, no limitations within her daily functioning. During audition she experienced that other auditioners were also hypermobile, thin and sometimes even performed better than herself. Troubled that she may not be able to stand out from or even keep up with the other students in class, she has started to practice extra hours.

Some clinical questions that come to mind:

- How is Anne guided during her pubertal maturation process with her joint hypermobility in a challenging dance company?
- What are the possible functional- and psychosocial consequences if Anne remains generalized hypermobile in her joints?
- How should local dance schools and professional dance educations guide young professional dancers in excelling in dance during and after puberty?
- Are the staff and lecturers aware of the presence of generalized joint hypermobility (GJH) and possible presence of hypermobility of other soft tissues within their students and the (dis)advantages?
- When does one have "just" GJH as being above average on the normality scale for joint mobility and where does pathology or disability start?

Generalized joint hypermobility

Joint hypermobility is characterized as a condition where an individual's synovial joint exhibits a range of motion exceeding the typical limits, accounting for factors such as age, gender and ethnic background.[1] Prevalence of Generalized Joint Hypermobility (GJH) varies from 2–55%[2–5] in children and adolescents and 5–43% in adults,[4,5] contingent of race, age, gender, and the used diagnostic tool. Some children benefit from their joint hypermobility, allowing them to excel in sports, dance or music. Others instead develop muscle and joint problems or develop systemic symptoms such as chronic fatigue, abdominal discomfort, or signs of dysautonomia.[6] Joint hypermobility can occur either generalized or localized, and both can lead to systemic complaints. Localized Joint Hypermobility can be acquired over time through activities like training and stretching, as observed in baseball, ballet, gymnastics or playing a musical instrument where these ranges are required to be able to excel and reach the top, and as such in these conditions can be experienced as an advantage.[7–9]

The spectrum of generalized joint hypermobility

It is not yet clear whether GJH is the end of the normal spectrum of joint range of motion or whether it is a polygenic group at the mild end of the spectrum of Hereditary Connective Tissue Disorders (HCTDs).[10] Genetic causes of GJH include HCTDs such as Marfan Syndrome (MFS), Loeys-Dietz Syndrome (LDS), Ehlers-Danlos Syndrome (EDS), Osteogenesis Imperfecta, or an inherited skin disorder (e.g. Cutis Laxa). Depending on the type of collagen affected, mutations can lead to various disorders, such as the Ehlers-Danlos syndromes (EDS) associated with collagen types I, III, or V. The Ehlers-Danlos syndromes represent a diverse group of inherited connective tissue disorders characterized by traits like GJH, skin hyperextensibility, and tissue fragility in various parts of the body, including the skin, joints, internal organs, and blood vessels.[11] Originally classified under the Berlin classification in 1986 with 11 numbered subtypes, it was subsequently revised in 1997 using the Villefranche nosology, which distinguished six subtypes based on clinical features, the presence of biochemical abnormalities, and known molecular defects, each subtype having major and minor clinical diagnostic criteria. In 2017, due to the discovery of new gene mutations and the need for a more precise clinical classification of the hypermobility type of EDS, a new international classification was established.[12]

Table 1.1. 2017 International Criteria for hEDS according to Malfait et al.[12]

Criterion 1: generalized joint hypermobility	Criterion 2: ≥2 of the three features (A, B, C) have to be present:	Criterion 3: all three need to be met:
Positive Beighton score (0/9)*= - ≥6 in pre-pubertal children and adolescents - ≥5 in pubertal men and women to < age of 50 - ≥4 in men and women > age of 50 *If Beighton score is one point below these cutoffs, two or more criteria of the Five-Point Questionnaire need to be positive	**Feature A = systematic manifestations of heritable connective tissue disorder** (positive when ≥5 are present) - Unusually soft or velvety skin - Mild skin hyperextensibility - Unexplained striae (such as striae distensae or rubrae at the back, groins, thighs, breasts and/or abdomen in adolescents, men or prepubertal women without history of significant gain or loss of body fat or weight) - Bilateral piezogenic papules of the heel - Recurrent or multiple abdominal hernia(s) (e.g. umblical, inguinal, crural) - Atrophic scarring (involving ≥2 sites and without the formation of truly papyraceous an/pr hemosideric scars as seen in classical EDS)\Pelvic floor, rectal, and/or uterine prolapse (in children, men or nulliparous women without a history of morbid obesity or other known predisposing medical condition) - Dental crowding and high or narrow palate - Arachnodactyly (as defined in one or more of the following: (i) positive wrist sign (Steinberg sign) on both sides; (ii) positive thumb sign (Walker sign) on both sides) - Arm span-to-height ≥1.05 - Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria - Aortic root dilatation with Z-score >+2 **Feature B = positive family history** ≥1 first-degree relatives independently meet the 2017 Criteria for hEDS **Feature C = musculoskeletal complications (positive when ≥1 are present)** - Musculoskeletal pain in ≥2 limbs, recurring daily for at least 3 months - Chronic, widespread pain for ≥3 months - Recurrent joint dislocations or frank joint instability, in the absence of trauma (a or b) a. ≥3 atraumatic dislocations in the same joint or ≥2 atraumatic dislocations in two different joints occurring at different times b. Medical confirmation of joint instability at ≥2 sites not related to trauma	1. Absence of unusual skin fragility, which should prompt consideration of other types of EDS 2. Exclusion of other heritable and acquired connective tissue disorders, including autoimmune rheumatologic conditions. In patients with an acquired connective tissue disorder (e.g. lupus, rheumatoid arthritis, etc.), additional diagnosis of hEDS requires meeting both Features A and B of Criterion 2. Feature C of Criterion 2 (chronic pain and/or instability) cannot be counted towards a diagnosis of hEDS in this situation. 3. Exclusion of alternative diagnosis that may also include joint hypermobility by means of hypotonia and/or connective tissue laxity. Alternative diagnoses and diagnostic categories include, but are not limited to, neuromuscular disorders (e.g.) myopathic EDS, Bethlem myopathy), other HCTD (e.g. other types of EDS, Loeys-Dietz syndrome, Marfan syndrome) and skeletal dysplasias (e.g. OI). Exclusion of these considerations may be based upon history, physical examination and/or molecular genetic testing, as indicated.

This classification recognizes 13 subtypes with the hypermobile type (hEDS) being the most prevalent. The genetic basis of hEDS remains largely unknown and diagnosis relies solely on clinical findings.[13] Presently, hEDS diagnosis is more stringent, requiring the simultaneous presence of three criteria (as outlined in Table 1.1).

First, it necessitates the presence of GJH, defined as the ability of several joints, in children and adolescents, to move beyond normal limits actively or passively. Second, signs of generalized tissue fragility (such as mitral valve prolapse, mild skin hyperextensibility, pelvic floor prolapse, and arachnodactyly), positive family history, and/or musculoskeletal symptoms (e.g., pain, dislocations, joint instability) must be present, whereas some disorders are primarily observed in adults. Lastly, other EDS types and connective tissue disorders, or conditions causing GJH should be excluded to establish an hEDS diagnosis.[12]

In 2017, consensus criteria were established for adults with hypermobile type Ehlers Danlos (hEDS)[12] and hypermobility spectrum disorders (HSD).[14] HSD is referred to all individuals who do not completely fulfill the criteria for hEDS and do not suffer from any other EDS type but still face symptomatic GJH.[14] So far HSDs are specified by the type of joint hypermobility; generalized, peripheral or localized and is referred to as G-HSD, P-HSD and L-HSD. The type of hypermobility is accompanied with at least one musculoskeletal manifestation from the new nosology but do not meet the full diagnostic criteria for hEDS or include the so called historical HSD, H-HSD including (all former EDS-HT or JHS) patients that self-reported (historical) GJH with a negative Beighton score accompanied by at least one musculoskeletal manifestation from the new nosology excluding other HSD types as well as other rheumatologic conditions.[14] HSD aims to reveal subtypes and close the gap between GJH and hEDS gaining recognition for clinically relevant manifestations that can seriously impact the quality of life and management of the affected individuals.[14]

The most common cause of GJH in children and adolescents is independent of an inherited connective tissue or other syndromic disorder and yet is not genetically detectable.[6] Because of the frequent occurrence of GJH in children, it is more difficult to differentiate between children who are physiologically hypermobile or those who have an underlying disorder. In addition, the degree of hypermobility decreases during childhood, in girls usually later than in boys.[15] Skin abnormalities or signs of connective tissue disease often develop over time (e.g., stretch marks, abnormal scar formation, hernia). Therefore, it was recently suggested by an international pediatric expert working group that the 2017 hEDS / HSD criteria should not be applied in children who are not yet mature.[6] A new diagnostic framework was created specifically for children and adolescents based on literature, international experts

and patient organizations that allowed for the changes that may occur during growth. This framework provides "fluid" descriptive diagnosis for children and adolescents with GJH. Depending on the development of symptoms and complaints, children and adolescents may be classified into different diagnostic groups over time. Symptoms may disappear, sometimes only the musculoskeletal symptoms persist, or symptoms may increase over time. The new diagnostic framework consists of 4 main categories and is based on the following clinical symptoms: (1) generalized hypermobility, (2) skin or other connective tissue abnormalities (3), musculoskeletal complaints, (4) the presence of co-morbidities, and is described in Table 1.2.[6]

Table 1.2. Diagnostic framework for pediatric joint hypermobility in the presence of skin abnormalities, musculoskeltal complications, and/or core morbid conditions[6]

	Generalized joint hypermobility	Skin and tissue abnormalities	Musculoskeletal complications	Core comorbidities
Asymptomatic				
Pediatric generalized joint hypermobility	Present	Absent	Absent	Absent
Pediatric generalized joint hypermobility with skin involvement	Present	Present	Absent	Absent
Symptomatic conditions				
Pediatric generalized joint hypermobility with core comorbidities	Present	Absent	Absent	Present
Pediatric generalized joint hypermobility with core comorbidities and with skin involvement	Present	Present	Absent	Present
Pediatric hypermobility spectrum disorder, musculoskeltal subtype	Present	Absent	Present	Absent
Pediatric hypermobility spectrum disorder, musculoskeltal subtype with skin involvement	Present	Present	Present	Absent
Peadiatric hypermobility spectrum disorder, systemic subtype	Present	Absent	Present	Present
Peadiatric hypermobility spectrum disorder, systemic subtype with skin involvement	Present	Present	Present	Present

Generalized joint hypermobility: functioning and health

While GJH may not cause complaints for some individuals, for others, it can lead to a wide range of problems, including soft tissue injuries, internal joint complications, arthritis, joint pain (arthralgias), or muscle pain (myalgias), resulting in functional disability and diminished societal participation and leisure and sport activities, prompting them to seek medical attention.[16,17] Currently, "Hypermobility Spectrum Disorders (HSD)" is used in adults as a descriptive and exclusion diagnosis. It is characterized by one or more musculoskeletal symptoms related to joint hypermobility, such as chronic pain, macrotrauma (dislocations, subluxations, or other soft tissue injuries), microtrauma, degenerative joint or bone disease, disturbed proprioception, muscle weakness, or other musculoskeletal features (e.g., pes planus, valgus deformity of elbows, scoliosis).[14] Limited soft tissue fragility related to joint hypermobility may also be present, although it does not meet the current diagnostic criteria for hEDS.[14]

In adults, four different HSDs can be distinguished based on the presence and extent of joint hypermobility. Generalized HSD (G-HSD) is characterized by generalized joint hypermobility (positive Beighton score) without hEDS diagnostic criteria, Peripheral HSD with GJH primarily in hands and feet (P-HSD). Localized HSD (L-HSD) is defined by joint hypermobility at a single joint, or a group of joints and historical HSD (H-HSD) is diagnosed when the Beighton score is negative but generalized joint hypermobility was self-reported in the past.[14]

It emphasizes that other causes for symptoms and complaints should be excluded: hereditary connective tissue disorders (HDCT), genetic syndromes, skeletal dysplasia, or neuromuscular diseases. The minimum age for applying the framework is 6 years, given the insufficient bone formation in younger children causing diagnosing difficulties. Full-grown adolescents and young adults of 18 years and older with GJH are classified according to the current 2017 criteria for h-EDS and hypermobility spectrum disorders (HSD).[12]

In addition to the degree of GJH, other organ systems composed of connective tissue should be assessed within the framework as shown in Table 1.3.[6]

Table 1.3. Assessment of other organ systems besides to the degree of GJH according to Tofts et al.[6]

Skin/connective tissue abnormalities	Musculoskeletal complications	Co-orbidities

Positive when 3 out of 6 symptoms are present;
 	
1. Conspicuously soft or velvety skin (subjective)
2. Excessive elasticy of the skin (to be tested on the volar side of the forearm – subjective)
3. Unexplained stretch marks on the back, groin, thighs, breasts or abdomen (without major weight changes)
4. Atrophic scarring (thin and deep scars/mild cigarette paper scars) in at least 1 location without true parchment-like an/or yellow-brown discoloration as seen in classic EDS
5. Bilateral piezogenic papules on the heels
6. Recurrent hernia, or a hernia in more than one location (excluding umbilical hernia)
	Positive if two or more of the following symptoms are present;
	
	- episodic pain related to activities
	- recurrent (sub)luxations or obvious joint instability
	- presence of soft tissue injuries such as sprains
		- Chronic pain
		- Chronic fatigue
		- Functional gastrointestinal complaints
		  - abdominal pain
		  - constipation
		  - diarrhea
		- Functional bladder complaints
		  - stress incontinence
		  - involuntary urine loss
		- Dysautonomia
		  - orthostatic intolerance
		  - postural orthostatic tachycardia syndrome (POTS) – in older adults

Generalized joint hypermobility: physical and psychological factors

First presentation of symptoms in GJH is frequently associated with like trauma, pregnancy, childbirth, unresolved previous joint problems or de-conditioning related to a passive lifestyle.[18] Complaints during childhood like joint pains in back and knees often accompanied with a history of growing pains or benign paroxysmal nocturnal leg pain are reported by many hypermobile individuals and may be a sign for hypermobility.[18] Participation in activities in activities such as ballet and gymnastics where immanent flexibility is considered beneficial may suggest joint hypermobility.[18]

A history of soft tissue injuries, joint pain, fractures, dislocation, and subluxations, particularly if they occur with minimal provocation and have been slow to resolve, may be a good indicator of generalized joint hypermobility. Exploratory questions about other areas of the body and body systems are essential. These systemic signs and symptoms may include urogenital problems (prolapse, incontinence), vascular problems (bruising, varicose veins,

low blood pressure), neural problems (clumsiness, unsteadiness, paresthesia, neuropathies.[18]

Individuals with GJH may not always exhibit symptoms. In fact, some even leverage GJH to excel in specific sports such as gymnastics, martial arts, or dancing. Conversely, others may encounter a range of musculoskeletal issues, including joint pain in multiple areas, fatigue, reduced motor skills, and muscle weakness, varying from mild to severe.[19]

Scheper et al. observed that GJH was independently linked to physical deconditioning, fatigue, and psychological issues among professional dancers. Surprisingly, these dancers, who typically benefit from GJH for executing intricate dance routines, demonstrated associations with adverse outcomes. In a longitudinal study in children with HSD/hEDS, the presence of multisystemic and psychosocial complaints and pain were most likely to have a subsequent debilitating trajectory towards impairments and disability.[6,20]

Physical factors

Muscle function is of great value in individuals with HSD, as impaired muscle function is associated with impaired physical functioning and activity and may compromise existing joint instability and consequently contribute to overload injuries and recurrent joint dislocations, and as such further compromise quality of life.[21]

Previous research has shown decreased muscle strength (maximal strength and strength endurance) in both upper (maximal muscle strength) and lower (maximal strength and strength endurance) limbs in children and adults with hEDS and G-HSD (diagnosed according to the new and previous diagnostic criteria), which could not be explained by muscle atrophy as no different muscle mass was found compared to controls.[21,22]

Several factors underlying this decreased muscle strength have been hypothesized: (1) pain, (2) fatigue, (3) decreased proprioception (4) exercise avoidance due to pain, fear of (sub)luxating, (5) impaired structural properties of connective tissue.[23]

Psychological factors

Knowledge from the research domain of chronic pain indicates that pain-related fear plays a disabling role in the development and maintenance of chronic musculoskeletal pain syndromes, such as hEDS.[24–26]

According to the fear-avoidance model (FAM), a biopsychosocial explanatory model for pain related disability, pain experience can be interpreted in two different ways. Most people

will experience pain as non-threatening and as part of a life experience. Consequently, a person will confront and accept pain and perform activities as usual thus maintaining his/her habitual activity pattern, regardless pain. But others will consider pain can as threatening based on catastrophic thoughts causing pain-related fear and anxiety, which in turn leads to avoidance behavior. Long-term avoidance may lead to disuse, depression and disability and these long-term consequences may decrease the pain threshold at which ensuing pain will be experienced, thus causing a vicious circle. Pain-related fear is also present in individuals with hEDS.[27–29]

In addition, fear of dislocation or joint instability may also influence functioning of anxious persons with hEDS and HSD. It can therefore be hypothesized that the presence of anxiety and/or fear will, in addition to physical factors, further disable persons with hEDS and HSD. In addition, whether this also accounts for adolescents and young adults with asymptomatic GJH is currently unknown.

Despite above mentioned evidence, the effects of GJH on physical performance remain inadequately understood. If the presumption of connective tissue laxity holds true, GJH should impact functional status, even in individuals expected to excel in functional ability, such as professional dancers. Functional status encompasses a multi-dimensional concept involving patient-oriented health outcomes, encompassing aspects of daily functioning, including physical, psychological, and social factors.[30]

Although often reported by patients and clinicians, the evidence of impairments on functional status in symptomatic GJH is limited, as well the evidence of factors influencing functional status. Weight bearing physical activities like standing, walking, and participating in sports and leisure activities might be physically demanding in subjects with symptomatic GJH.[31,32] Possibly due to the presence of pain, fatigue and reduced physical fitness that could negatively influence functional status.[33–35] However, the extent to which these factors contribute to functional status remains uncertain, including the factors that determine how professional dancers can leverage GJH for benefit rather than contributing to functional disability.

Generalized joint hypermobility: functioning and health using the ICF-CY

To understand physical and psychosocial functioning and health in adolescents with GJH, it is important to map everyday problems and indicate interactions between physical features, activities, participation, environmental and personal factors, HRQoL and mental

health. The United Nations Convention on the Rights of the Child defines "children" as those persons below the age of 18 years.[36] The WHO defines "adolescence" as the transitional stage of physical and psychological development that generally occurs during the period from puberty to adulthood.[37] Furthermore, other overlapping terms used by the WHO are "youth" defined as those persons between 15–24 years.

The International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY: from birth to 18 year of age) is a classification by which the functioning of children and youth can be described in detail from different perspectives, such as body functions, anatomical characteristics, activities, and participation.[37] ICF-CY also contains a classification of external factors, the immediate and wider environment of a child (Figure 1.1). ICF-CY is especially extended with learning and playing aspects and the developmental process. The model consists of five interacting domains: "Body functions and structures", "Activities", "Participation", "Environmental factors" and "Personal factors".

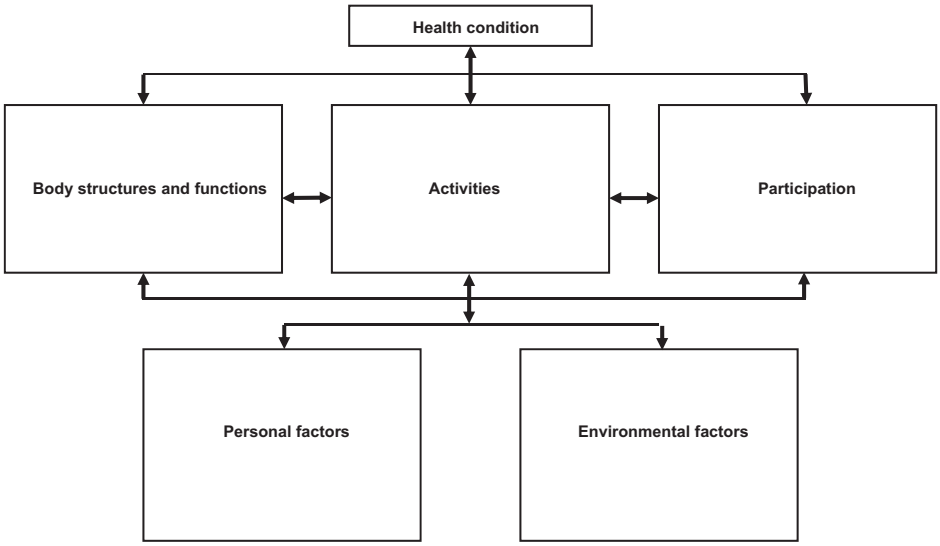

Figure 1.1. International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) model.[37]

In this model "Body Functions" are defined as physiological functions of body systems and "Body Structures" as anatomical parts of the body such as organs. Impairments are problems in body function or structure such as a significant deviation or loss. "Activity" is defined as the execution of a task or action by a child or adolescent. Activity limitations are difficulties a child may have in executing activities (mobility, selfcare, household tasks e.g.).

"Participation" refers to involvement in daily life. Participation restrictions are problems a child or adolescent experience in involvement in daily life situations (friendships, school, work, sport, leisure, playing). "Environmental factors" are defined as the physical, social, and attitudinal environment in which children live and conduct their lives (support and relationships, environmental attitudes, services, products, and technology). "Personal factors" include the particular background of a child's life, like gender, age, coping strategies, overall behavior pattern, planning, self-esteem, social background, education, and other factors that influence functioning. For adults, the International Classification of Functioning, Disability and Health (ICF) can be used.[38] The ICF-CY provides a common and global language and facilitates documentation of functioning, disability and health of children and adolescents.[37]

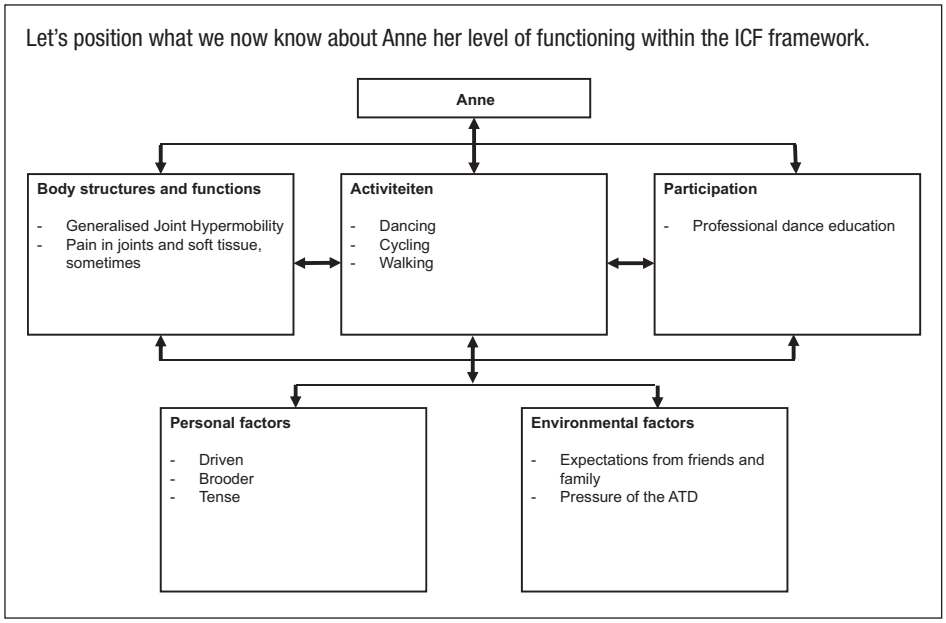

Figure 1.2. International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) model of Anne.

In (pediatric) physical therapy psychometric validated assessment tools should be used, regarding disease specific and generic problems within the different domains of the ICF-CY. Data should be compared with normative or reference values to contribute to clinical reasoning regarding the questions for help of the child, adolescence, and youth with (a)-symptomatic generalized joint hypermobility in the broad spectrum from "normality" towards "pathology".

Generalized joint hypermobility: assessment using the Beighton score

The Beighton score (BS) is considered the "gold standard" for assessing GH and consists of five standardized tests as visually expressed in Figure 1.3.[39-41]

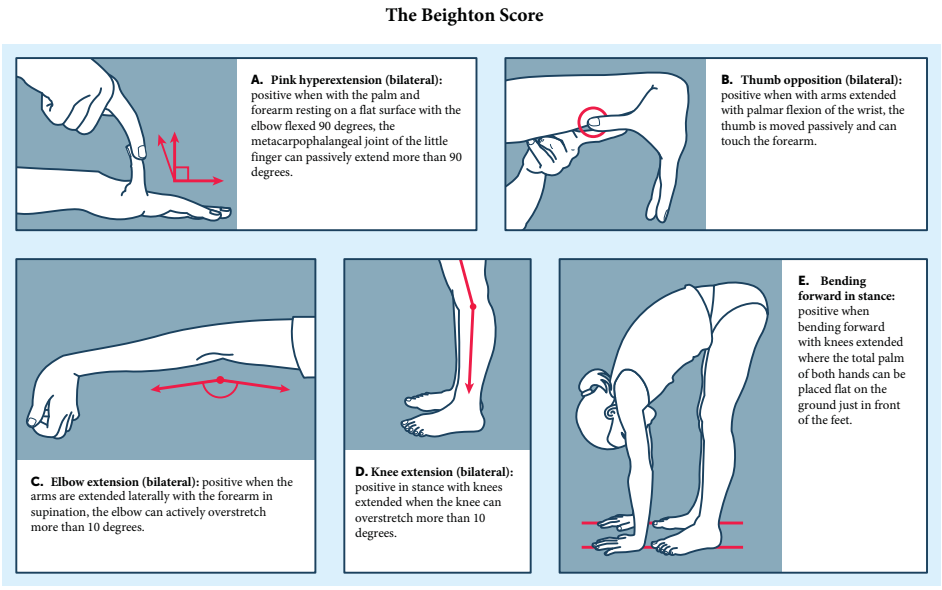

Figure 1.3. An illustration of the Beighton Score adapted with permission of M. Claassen, extracted from Engelbert et al.[41]

The total score ranges from 0–9 where (0: negative, 1: positive per site), with variable cut-off points for age. In children from 6 to 18 years of age, the BS can be taken and is referred to as GH at a score more or equal to 6, between 18 and 50 years of age at a score more or equal to 5, and over 50 years of age more or equal to 4. Because the BS measures only a few joints, an impression of all other joints should also be obtained. The BS is used for classification, however, children with local hypermobility of joints outside the BS (e.g., shoulder, hip, kneecap, and ankle) can also develop HSD. Because debate remains about the psychometric properties of the BS, other tests that measure more joints in different planes of motion are also being developed for children.[42–45]

At the University of Applied Science of Amsterdam (Faculty of Health) as well as in the Department of (Pediatric) Rehabilitation of the Amsterdam University Medical Center, the functional outcomes and consequences of GJH in the "normal" population, in highly

performing professionals, as well as in youth with HCTDs is focus of research regarding physical- and psychosocial functioning and societal participation. Strong collaboration with children, adolescents, and their parents, and with young adults and with national- and international allied health professionals and medical doctors, as well as patient societies is considered essential in the diagnostic and therapeutic process of participants with GJH and musculoskeletal-, systemic- and psychosocial complaints.

Aims and outlines of this dissertation

This dissertation studies the relation between anxiety and / or fear and GJH in adolescents and young adults. The second aim of this dissertation is to gain a better insight into the nature and prevalence of symptoms of anxiety in GJH and the impact on daily life functioning and participation. As diagnosis in children and adolescents with GJH are “fluid”, recognition of GJH and associated complaints is essential and the differential diagnostics towards HCTDs should be made. Additionally, this dissertation wants to contribute to the understanding of the different phenotypes and the changes within the clinical presentation in individuals with GJH and the disability they perceive.

Where one may have GJH without having any problems, others may, when injured, develop musculoskeletal- and more systemic problems causing disability. Therefore, we translated and validated a questionnaire, the Dutch Child Activity and Limitations Interview (DCALI) in **Chapter 2** to assess pain-related disability in adolescents with chronic pain. This questionnaire is proposed as a tool that might be suitable to assess pain-related disability in adolescents and youth with chronic musculoskeletal pain, including those with symptomatic GJH (HSD and hEDS) as well as HCTDs.

To evaluate the association between anxiety and GJH we conducted three different studies. First, to evaluate the presence and impact of symptomatic GJH and psychosocial characteristics like anxiety and / or fear in a nonclinical group of adolescents. We conducted a cross-sectional study in high performing adolescents and young adults who were professional dance students. We classified four groups based on the presence of GJH and/or anxiety and examined on physical- and psychosocial outcomes in **Chapter 3**.

Another study described the changes over time in physical functioning as muscle strength, endurance, fatigue, pain and psychosocial outcomes as anxiety and pain coping within the highly performing professional dance students of Chapter 3.

Chapter 4 presents the results of the measurements in the same group with a follow up of one year.

Finally, to gain insight in the associations between GJH, anxiety and pain, we performed a systemic review in **Chapter 5** presenting the state of the art in the literature regarding these associations in adolescents and adults. The current state of evidence regarding these associations is presented comparing adolescents with adults and distinguishing healthy individuals with GJH from individuals with HSD or (h)EDS.

In **Chapter 6**, the general discussion reflects on the main findings of the previous chapters, the important methodological considerations as well as the strengths and limitations as well as the recommendations for the educational, clinical, and scientific implications for clinical care and future research.

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Chapter 2

The Dutch version of the self-report Child Activities and Limitations Interview in adolescents with chronic pain

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Abstract

Purpose: To assess the factor structure, related constructs and internal consistency of the Child Activity Limitation Interview 21-Child version for use in Dutch-language countries.

Methods: Cross-sectional validation study: After forward and back translation of the Dutch version of the Child Activity Limitation Interview 21-Child adolescents (11–21 years old) with chronic musculoskeletal pain completed an assessment. The assessment contained the Dutch Child Activity Limitation Interview, and questionnaires about demographics, pain intensity, functional disability, anxiety and depression. Internal consistency and construct validity were evaluated through exploratory factor analysis (principal axis factoring with oblique rotation) and hypotheses testing using pain intensity, activity limitations, anxiety and depression as comparative constructs.

Results: Seventy-four adolescents completed the assessment. Exploratory factor analysis resulted in a two-factor structure, explaining 50% of the variance. Internal consistency was good (Cronbach's α=0.91 total scale, α=0.90 Factor 1, α=0.80 Factor 2). All nine hypotheses were confirmed.

Conclusion: The Dutch version can be used to assess pain related disability in Dutch-speaking adolescents comparable to the study sample. Scores on both subscales provide insight into the severity of the pain-related disability in both daily routine and more physically vigorous activities.

Implications for rehabilitation

- Chronic pain is a disabling disorder which not only impacts physically but restricts quality of life.
- This study provides clinicians a questionnaire to measure pain-related disability and quantify the impact of pain on the daily living of adolescents.
- The advantage of the Dutch version of the Child Activity and Limitations Interview over other measurements is that is can distinguish limitations in daily activities from more physically vigorous activities.

Introduction

Chronic musculoskeletal pain without an underlying disease is considered a common problem, affecting 4–40%[1] of children and adolescents. Girls are more likely to develop chronic pain complaints than boys.[2,3] Adolescents with chronic musculoskeletal pain experience limitations participating in normal age-appropriate activities such as attending school, social- and leisure activities, sports and social interactions with peers and family.[4] Due to rapid psychosocial development and maturation in childhood, the normal age-appropriate activities are changing constantly, which makes it very difficult to recognize limitations in activity and participation due to pain. Currently, instruments to measure pain related disability in adolescents are not available to be applied in a Dutch speaking population. If pain-related disability could be assessed in adolescents with chronic musculoskeletal pain it would give more insight in the types of activity limitations in adolescents.

So far only one questionnaire has been specifically developed for screening pain related disability in adolescents; the Child Activity Limitations Interview (CALI21-C).[5,6] The CALI21-C is an English self-report questionnaire and was derived from the original Child Activity Limitations Interview. Where the score of the original CALI only include the eight most difficult item the CALI21-C measures the pain-related limitations and distinguishes daily routine- and more physically vigorous activities. The modification to a self-report questionnaire increased flexibility when an interview was not possible. The English self-report CALI21-C has been examined on its factor structure as being an aspect of construct validity but it has not yet been translated and validated in a Dutch-language population. A total number of 21 items in the CALI21-C captures concepts of sleep and rest, eating, school, ambulation, mobility, work related tasks and physical, social and recreational interactions. The original English CALI21-C has demonstrated good internal consistency and construct validity in youth with a variety of chronic pain conditions, like back-, abdominal- and musculoskeletal pain, recurrent headaches, juvenile idiopathic arthritis and sickle cell disease.[5,6] The advantage of the CALI21-C to other frequently used instruments is that it not only recognizes limitations in activity and participation but it can also distinguish pain-related disabilities affecting activities of daily living from more physically vigorous activities, such as running and sports.

The focus in the current assessment of pain-related disability in youth consist of a set of rather generic instead of disease-specific questionnaires. Although questionnaires like the Functional Disability Inventory[7,8] (FDI) are frequently used, they were originally not designed for daily report of pain-related disability in youth. Often limitations in activities

are related to "overall health" or do not contain subscales concerning different domains in activity, which makes it difficult to gain a more detailed insight in the impact of chronic musculoskeletal pain on the daily life.

The aims of the present study were to establish: (1) the factorial structure, (2) the construct validity, (3) the internal consistency of the CALI21-C after translation in the Dutch language (DCALI).

Methods

Participants and procedures

Data was collected at the Department of Rehabilitation Medicine at Maastricht University Medical Center between January 2013 and July 2014. In total 94 adolescents with chronic musculoskeletal pain visiting the department of rehabilitation medicine were invited to participate. After initial intake by a consultant in rehabilitation medicine, the adolescents were invited to complete a digital screening set of self-report questionnaires. For the purpose of the validation study, the translated DCALI was added to the screening questionnaires. The aim of the intake is to gain insight in the level of functioning and the impact of pain on the adolescent's life and to identify facilitating and disabling factors for changing the current situation with pain. The adolescents received a link enclosed in an email with a personal login code, allowing the participants to complete the questionnaire at home.

For eligibility, chronic musculoskeletal pain was defined as having musculoskeletal pain complaints with a duration over 3 months. Furthermore, no specific somatic (rheumatic, neurological and orthopaedic) conditions could be diagnosed as the cause or severity of the current pain complaints. The Medical Ethical Committee University Maastricht approved of the study (NL41712.068.12/METC12-3-052) and the consent procedure. Participants consented for the use of the data for scientific research.

Measures

Pain-related disability The CALI21-C is a measure to assess functional disability due to chronic pain in school-age adolescents. The original measure demonstrates sound psychometric properties.[5,6] The original English version of the CALI21-C consists of 21 items capturing seven concepts, which should encounter the broad range of age-appropriate activities of school-aged children. Each item is scored over the previous 4 weeks, rating the difficulty in participating in each activity on a five-point Likert scale, ranging from 0 "not

difficult" to 4 "extremely difficult". Total score ranges from 0 to 84 where higher scores indicate greater activity limitation or more impairment due to pain.

In the original version two subscales were found, "Routine" (five items, α=0.73) and "Active" (eight items, α=0.93). The routine subscale indicates difficulties with basic activities of daily living and learning tasks like "Going to school" or "Reading". The active subscale includes more vigorous physical activities, which require higher levels of functional ability like "Sports" and "Riding a bike or scooter". The CALI21-C showed a high level of internal consistency (α=0.95) and revealed relationships with measures of pain intensity and depressive symptoms (moderate correlation, r ranged between 0.42–0.58). Confirming the hypothesis that the CALI21-C would be moderately related to measures of pain symptoms, anxiety and depression.[5,6]

Translation procedure

The CALI21-C was originally an English questionnaire. A Dutch version was systematically produced by a translation process. A first translator translated the questionnaire in Dutch. Then a native English speaker translated this Dutch version back into the English language. After comparison of the English translation and original English questionnaire the final Dutch translation was accepted by the authors. Translation of the CALI21-C into a Dutch version was not part of this study.

Comparator measures

Activity Limitations The Functional Disability Inventory (FDI) is a self-report inventory for adolescents and measures activity limitations by 15 items over four domains, school, home, recreation and social interactions.[9] The items are rated on a five-point Likert scale ranging from 0 "no trouble" to 4 "impossible" where higher total scores indicate greater amount of activity limitations. The FDI was designed to be applicable to a broad range of diseases and varying levels of severity of activity limitations. The original FDI was validated in children with abdominal pain at an American University Medical Centre and showed a high internal consistency (α ranging from 0.86–0.91) with moderate-to-high test-retest reliability (0.74).[9] Furthermore, the FDI is also found to be a significant predictor of pain, school-related disability somatic and depressive symptoms.[9] Although the Dutch version of the FDI is a frequent used questionnaire, any cross-cultural validation has not yet been performed.[7–9]

Depressive symptoms Depressive symptoms were measured by the Dutch version of the Child Depression Inventory (CDI).[10–12] The CDI is a self-report inventory that assesses

symptoms of depression in children and adolescents aged 7–18 years. It contains 27 items on five subscales respectively negative mood, interpersonal problems, ineffectiveness, anhedonia and negative self-esteem, representing depressive symptoms. Respondents are asked to choose one description out of three that best fits how they have been feeling over the past 2 weeks. Descriptions to choose from are "I do most things well", "I do most things wrong" and "I do everything wrong" scored on a scale from 0 to 2 with total CDI scores ranging from 0 to 54. Higher scores indicate higher levels of depressive symptoms. Timbremont et al.[11] found the CDI to have a high internal consistency α=0.85 in a nonclinical and α=0.86 in a clinical sample. The original English CDI subscales have shown good-to-fair internal consistency, negative mood α=0.62, interpersonal problems α=0.59, ineffectiveness α=0.63, anhedonia α=0.66 and negative self-esteem α=0.6810. Reliable and valid norms for its utility as a screening instrument for depression in both clinical and nonclinical youths are available in the Dutch version.[10,13]

Pain intensity

Pain intensity was measured by a 10 cm Visual Analogue Scale ranging from "no pain" to "the worst pain I can imagine". The average score of three VAS scales measuring the current level of pain, the worst pain in the past week and the least pain in the past week. Pain severity measured by VAS has good reliability and validity among individuals as young as 9 years.[14,15]

Data analysis

Data analysis was performed using SPSS version 23.0 (IBM Corp, Armonk, NY). The digital set of questionnaires alerted adolescents in case of unanswered questions. Missing items were not replaced.

Analysis of factor structure and internal consistency After translation the CALI21-C was approached as a "new" instrument. Exploratory factors analysis was conducted to investigate latent constructs within the broader domain of activity.[16] All 21 items of the DCALI were investigated for normality of the scoring distribution. Inter-item correlations were calculated to investigate for a lack of correlation and multicollinearity (inter-item correlation $0.2<r<0.9$) in the correlation matrix.[17] In case of high inter-item correlations on the correlation matrix ($r>0.75$) the underlying constructs were discussed between the authors. If it was concluded that underlying constructs were similar one of the items was excluded. Corrected item-total correlations for all DCALI items were calculated. Principal axis factoring is used as extraction method. Assessment of the number of factors was examined by the

Kaiser's criterion[18] (the eigenvalue represents the amount of variation explained by a factor) and interpretation of the Scree plot. The original CALI21-C consisted of two factors, which the authors expected to be similar in the translated version. A 1-, 2- and 3-factor structure on meaningfulness of the factors was investigated. Items with one factor loading >0.4 and a loading <0.4 on other factors were directly included.[19] Items loading <0.4 were individually assessed on clinical relevance. If an item loaded on multiple factors the classification of the item to a certain factor was based on the relation of the underlying construct of the item with the construct of the factor. Factor structure was established by the use of oblique promax rotation as the subscales were known to correlate in the original CALI21-C.[6] Sampling adequacy and internal consistency were evaluated by Kaiser-Meyer-Olkin and Cronbach's α. Values of Cronbach's α between 0.70 and 0.95 are considered good.[20]

Conceptual framework and hypotheses for evaluation of construct validity

To assess construct validity, the scores of the DCALI were correlated with scores of theoretically more or less related measures, being the FDI,[7,8] pain intensity measured by a VAS[15] and the CDI.[13] Escorpizo et al.[21] has described pain, in adults, as a musculoskeletal condition and classified musculoskeletal-related disability as complex and multifaceted. Musculoskeletal-related disability is spread over the different horizontal domains of the ICF and can be influenced by contextual factors. Within the ICF model the authors have situated pain-related disability primarily in the activity and participation domain and have linked it to both the "body structures and functioning" (BSF) domain, for pain intensity, and the contextual domain, to encompass the feeling of being disabled due to pain. Functional disability (FDI) is a construct closely to pain-related disability and situated in the same domain, however it differs from the broader construct of pain-related disability which also includes the feeling of pain, situated in the BSF domain, and encompasses the perception of disability, situated in the contextual domain. In validation studies, the FDI has been found to have positive but moderate correlations with pain and somatic and depressive symptoms, where higher levels of disability are often seen associated with somatic and depressive symptoms.[9] In line with previous research it is hypothesized that higher levels of functional disability correlate highly positive ($0.7<r\leq0.9$) with higher levels of pain-related disability.[5,6] Pain intensity (VAS), anxiety and depression (CDI) are known to be associated with higher levels of disability in physical fitness, psychological- and social functioning in children.[22,23] However, these constructs belong to the BSF contextual domain and not to the activity and participation domain in which pain-related disability is situated. The authors think that pain intensity, anxiety and depression can as described by Escorpizo et al.[21] influence pain-related disability but this association has not yet been established

in adolescents. Therefore, it is hypothesized that DCALI total and subscale scores have weak-to-low positive correlations (0<r<0.5) with VAS and CDI. All hypothesized strengths and directions of the correlations are expressed in Table 2.1.

Table 2.1. Hypothesized strengths of correlations between DCALI-C and construct variables

	Pain intensity	CDI	FDI	FDI physical activity	FDI daily activities
DCALI total	0<r<0.5	0<r<0.5	0.7≤r<0.9		
DCALI active	0<r<0.5	0<r<0.5		0.7≤r<0.9	
DCALI routine	0<r<0.5	0<r<0.5			0.7≤r<0.9

The theoretical construct definitions and the strength of the hypothesized correlations are based on the original validation study.[5] In the original study, the two subscales were found and showed to be correlated with each other (r=0.44). It is expected that in the DCALI has a similar two factor structure with the two subscales correlating moderately with each other.

Analysis of construct validity

To assess construct validity, based on formulated hypotheses, correlations between DCALI and the other measurements were calculated. Based on the distribution of the item scores, Spearman correlation coefficients were compared to the hypothesis as stated in Table 2.2. Construct validity was determined with >75% of the hypotheses confirmed.[20]

Results

Clinical characteristics

Sociodemographic and pain-related characteristics of the participants are presented in Table 2.2. Twenty participants were excluded from the analysis, because they completed none of the questionnaires in the digital set of questionnaires. Scores of seventy-four participants, (66 girls) with a mean age of 16 years completed the digital set of questionnaires and were included in the analysis. All participants had chronic musculoskeletal pain in varying body parts, in 51% of the participants the pain started between 1 and 5 years ago. Table 2.3 reports on the average scores on all four measurements used in this study.

Factor structure

Normality within the scoring of the DCALI items was assumed after eyeballing of the data investigating skewness (range -1.12 to 2.96) and kurtosis (range -1.39 to 8.47). An overview

of the item scoring is shown in Supplementary Table S2.1. Items 3, 8, 12, 16 and 17 didn't use the entire range of the answering scale. On average, 31% (8–85%) of the participants scored in the lowest answering category of the Likert scale. Cumulatively, 50% of the participants scored on the lowest two answering categories, meaning that they either had no difficulties or little difficulties with the type of activities and participation in the items. The highest answering category was answered on average 15% (0–46%).

Table 2.2. Clinical characteristics

Characteristics	
Age (mean, SD, range)	16 (3), 11–21
Gender (*N*, % female)	66 (89%)
Educational level (*N*, %)	
Elementary school	5 (9.5%)
Lower general secondary education	10 (13.5%)
Higher general secondary education	16 (21.6%)
Pre university education	15 (20.3%)
Vocational education	12 (16.2%)
University of applied sciences	6 (8.1%)
University	1 (1.4%)
Current school participation (*N*, %)	67 (90.5%)
School absences in the past year (*N*, %)	
0–14 days	30 (40.5 %)
15–30 days	14 (18.9%)
1–3 months	15 (20.3%)
>3 months	13 (17.6%)
Missing	2 (2.7%)
Pain related characteristics	
Onset of current pain complaints (*N*, %)	
<3 months ago	2 (2.8%)
3–6 months ago	4 (5.4%)
6–12 months ago	15 (20.3%)
1–5 years ago	38 (51.4%)
<5 years ago	9 (12.2%)
Missing	6 (8.1%)
Type of pain problem	
Generalized pain problem / Fibromyalgia / hypermobility syndrome	24 (32.4%)
Complex Regional Pain Syndrome	7 (9.5%)
Chronic back pain / Whiplash	18 (24.3%)
Pain in upper extremities	5 (6.8%)
Pain in lower extremities	14 (18.9%)
Undefined	5 (6.8%)
Significant other person with chronic pain complaints (*N*, %)	23 (31.1%)

Table 2.3. Descriptive statistics of all study variables

	Total *N*=74		
	Mean	SD	Range
DCALI-C, (0–80)	28	13	2–55
DCALI-C Active, (0–50)	20	9	0–37
DCALI-C Routine, (0–30)	8	5	0–18
FDI, (0–75)	22	10	2–44
FDI Physical Activities, (0–40)	14	6	1–27
FDI Daily Activities, (0–35)	8	5	0–19
CDI, (0–54)	10	6	1–29
Pain Intensity, (0–100)	54	26	0–100

The correlation matrix was investigated for correlations <0.2 and >0.9 with item-total correlations ranged between -0.02 and 0.83. Inter-item correlations above 0.75 are shown in Table 2.4 and were discussed by the authors. Item correlations between item 2 “Gym” and 5 “Sports” and between 5 and 14 “Running” considered to have overlap as sport is a broader construct. The authors considered that both “Gym” and “Running” are adding clinical relevant information on the type of activity and participation. The constructs of items 7 “Playing with friends” and 12 “Doing things with friends” are similar but the authors consider them to differ between primary school aged children (item 7) and older children (item 12). Item 1 “Going to school” and item 21 “Being up all day (without a nap or rest)” seemed similar in the DCALI, it is suggested to rephrase item 21 into “Spending the day without a nap”. Because of their clinical relevance these items were kept within the analysis. Item 11 “After school practices” was eliminated from the sample based on collinearity with item 12 and 13 “Going to clubs/church activities” and the limited information in relation to the other items. Many inter-item correlations were <0.2, but all items correlated with at least 1 other item.[24]

The remaining 20 translated items were entered in the exploratory factor analysis using an extraction method of principal axis factoring with a promax rotation. Results are shown in Table 2.5. Kaiser-Meyer-Olkin measure was (0.82) and Bartlett’s Test[24] was significant ($p<0.001$). The Cattel’s Elbow criterion identified a two-factor structure explained 50% of the variance. Four items (item 10, 16, 17 and 19) had loadings <0.4 and were therefore not included in the analysis. This resulted in a 16-item Dutch version of the DCALI, containing 10 items in Factor-1, which could be labeled as “Active” subscale and 6 in Factor-2, which could be labeled as “Routine” subscale.

Internal consistency was calculated, resulting in a Cronbach's α of 0.91 for the total scale (16 items), Cronbach's α of 0.90 for Factor 1 and Cronbach's α of 0.80 for Factor 2.

Table 2.4. Multicollinearity in inter-item correlations.

Items	Dutch	English	Pearson	Item eliminated	Construct
1	Naar school gaan	Going to school	0.752	-	Item 21 should be rephrased.
21	De hele dag op school zijn (zonder een dutje te doen of te rusten)	Being up all day (without a nap or rest)			
2	Gymnastiek	Gym	0.757	-	Both items contain sports, in Dutch "gym" means sports activities in primary school whereas "sporten" is mainly focused on sporting activities not related to school.
5	Sporten	Sports			
5	Sporten	Sports	0.767	-	"Hardlopen" is considered both a sporting activity as well as a motoric movement.
14	Hardlopen	Running			
7	Met vrienden spelen/omgaan	Playing with friends	0.847	-	Both items focus on doing things with friends although "spelen met vrienden/ omgaan" related more to primary school aged children and "dingen doen met vrienden" to older children.
12	Dingen doen met vrienden	Doing things with friends			
11	Naschoolse activiteiten	After school practices	0.753	11	Both items focus on time spent after school. Item 12 is providing more information.
12	Dingen doen met vrienden	Doing things with friends			
11	Naschoolse activiteiten	After school practices	0.770	11	Both items focus on time spent after school. Item 13 is providing more information.
13	Naar clubjes/ verenigingen gaan	Going to clubs/ church activities			

Table 2.5. CALI Exploratory factor analysis results

Item n0.	Dutch item	Original English item	Classification Dutch item based on theory [a]	Classification English item based on EFA [b]	Mean (SD)	Corrected item-total correlation	Factor 1	Factor 2
5	Sporten	Sports	A	A	2.80 (1.29)	0.611	**1.023**	
14	Hardlopen	Running	A	A	2.89 (1.38)	0.665	**0.862**	
2	Gymnastiek	Gym	A	A	2.81 (1.37)	0.625	**0.852**	
18	Een of twee blokjes omlopen	Walking one or two blocks	A	A	1.35 (1.24)	0.639	**0.742**	
20	Fietsen of scooter rijden	Riding a bike or scooter	A	A	2.05 (1.35)	0.648	**0.675**	
6	Het doen van een hobby	Doing a hobby	-	-	2.08 (1.35)	0.547	**0.564**	
15	De trap oplopen	Walking up stairs	A	A	1.70 (1.21)	0.557	**0.514**	
12	Dingen doen met vrienden	Doing things with friends	-	-	1.43 (1.09)	0.739	**0.479**	0.430
13	Naar clubjes/verenigingen gaan	Going to clubs/ church activities	-	-	1.65 (1.45)	0.679	**0.472**	
7	Met vrienden spelen/omgaan	Playing with friends	A	A	1.24 (1.11)	0.666	**0.425**	
3	Lezen	Reading	R	R	0.65 (0.97)	0.380		**0.859**
4	Huiswerk	Schoolwork	R	R	1.30 (1.33)	0.427		**0.695**
8	TV kijken	Watching TV	R	R	0.47 (0.62)	0.229		**0.607**
21	De hele dag op school zijn (zonder een dutje te doen of te rusten)	Being up all day (without a nap or rest)	R	-	2.19 (1.52)	0.626		**0.556**
1	Naar school gaan	Going to school	R	R	1.93 (1.31)	0.640		**0.467**
9	Huishoudelijke taken of klusjes	Housework or chores	A	A	1.54 (1.16)	0.591		**0.433**
	Eigenvalues						6.624	4.985
	Variance (%)						38.647	11.566
	Cronbach's Alpha (*N*=74, 0% missing)						0.903	0.799

[a] Based on definitions of constructs. Active (A) and Routine (R).

[b] Based on factor structure of the original validation. Active (A) and Routine (R).

The bold values represents the allocation of the item to factor 1 or factor 2.

Hypotheses testing for construct validity

All comparator measurements were positively correlated with higher levels of pain-related disability. The calculated correlations in hypothesis testing were presented in Table 2.6. As hypothesized, highest positive correlations were found between total and subscale scores of the DCALI and the closest construct within the same ICF domain, activity limitations measured by the FDI. As hypothesized the DCALI total score correlated highly with total activity limitations (FDI; r=0.85). The DCALI active subscale correlated highly with the physical activity subscale of the FDI (r=0.83) and the DCALI routine subscale correlated highly with the daily activities subscale of the FDI (r=0.82) as hypothesized.

Moderate positive correlations between anxiety and depression (CDI) and pain-related disability total scale and subscales were found to be low, DCALI total score; r=0.34, p<0.01, DCALI Routine; r=0.39, p<0.01 and DCALI Active; r=0.26, p<0.05. Correlations between pain intensity and pain-related disability total and subscales were low to moderate, DCALI total score; r=0.45, p<0.01, DCALI Routine; r=0.39, p<0.01 and DCALI Active; r=0.26, p<0.05). Subscales of the DCALI were correlated 0.55 as hypothesized.

Table 2.6. Construct validity, Spearman correlations between DCALI and construct variables

	1. DCALI	2. DCALI active	3. DCALI routine	4. CDI	5. Pain intensity	6. FDI	7. FDI physical activity	8. FDI daily activities
1. DCALI	-	0.93*	0.80*	**0.34***	**0.45***	**0.85***	0.78*	0.72*
2. DCALI Active		-	0.55*	**0.26****	**0.45***	0.79*	**0.83***	0.53*
3. DCALI Routine			-	**0.39***	**0.33***	0.68*	0.45*	**0.82***
4. CDI				-	-.08*	0.36*	0.24**	0.45*
5. Pain intensity					-	0.50*	0.48*	0.42*
6. FDI						-	0.91*	0.83*
7. FDI Physical Activity							-	0.55*
8. FDI Daily Activities								-

DCALI-C, total score on the Child Activity and Limitation Interview; DCALI-C Active, subscale score on the Activity domain of the Child Activity and Limitations Interview; DCALI-C Routine, subscale score on the Routine domain of the Child Activity and Limitation Interview; CDI, total score on the Child Depression Inventory; Pain Intensity, average rating of pain at this moment, worst pain in the past week and least pain in the last week measured on a 10cm visual analogue scale: FDI, total score on the Functional Disability Inventory, FDI Physical Activity, subscale score on the Physical Activities domain of the Functional Disability Inventory; FDI Daily Activities, subscale score on the Daily Activities of the Functional Disability Inventory.
Bold values show the confirmed hypothesis.
** p<0.05 (two-tailed).
* p<0.01 (two-tailed).

Discussion

To enable the use of the CALI21-C in Dutch-speaking adolescents with chronic musculoskeletal pain, the internal consistency and aspects of construct validity of the Dutch translation of the CALI21-C were evaluated. Exploratory factor analysis showed a two-factor structure in the Dutch version of the CALI21-C. Good internal consistency, Cronbach's α>0.80, was found in the total scale (16 items) and both in the active subscale (10 items) and routine subscale (6 items) of the DCALI.[20] With all nine hypotheses confirmed in hypotheses testing construct validity was evaluated as excellent.[20] Relationships turned out as hypothesized with the Routine subscale having slightly stronger correlation with anxiety and depression symptoms then the Active subscale. Based on consistent psychometric properties, the DCALI is advised in measurement of pain-related disability in adolescents with chronic pain that were treated in rehabilitation care in the Netherlands.

These findings are in line with the results in the original validation of the CALI21-C.[5] The Dutch version of the CALI21-C resulted after the exploratory factor analysis in a 16-item two-factor structure with an Active subscale of 10 items and a Routine subscale of 6 items. These factor loadings slightly differ from the original child version, which consisted of 13 items with 8 items in the Active subscale and a Routine subscale of 5 items. Item 6 "Doing a hobby", item 12 "Doing things with friends" and item 13 "Going to clubs/church activities" were added to the Active subscale and item 9 "Housework or chores" and item 20 "Being up all day" loaded in the Routine subscale while it was loaded in the Active subscale in the original version. Item 16 "Eating regular meals" did not load in both factors while it was loaded in the Routine factor in the original version whereas item 21 "Being up all day without a nap or rest" did load on the Routine subscale where it was not loaded on any factor in the original version.

Labelling the two factors similar as in the original version seemed legitimate considering that the majority of the items in both Active and Routine subscale met up to the original definitions, respectively physically vigorous activities and routine activities of daily living. Our sample included adolescents with chronic musculoskeletal pain from an academic medical centre with chronic musculoskeletal pain on different body parts. The original sample also included paediatric pain patients with headaches and abdominal pain. Furthermore, the majority of our sample chronic musculoskeletal pain patients was female (86%), as similar to the Dutch population. In contrast to the original sample were only 58% was female.

Both subscales as well as the total scale of the DCALI had a high internal consistency, with all a Chronbach's α<0.80. The small difference in the internal consistency of both subscales and the total scale might be explained by the reduction of items in the DCALI.

It is important to note that within this study there are some limitations. It was chosen to approach the translated DCALI as a "new" measurement tool and therefore exploratory factor analysis was performed to determine the factor structure. The high Kaiser-Meyer-Olkin measure provided foundation to perform factor analysis but due to the limited sample size of only 74 participants a confirmatory factor analysis was not performed.[17] Furthermore, the scoring by the five-point Likert scale of the DCALI was assumed be a continuous variable. Therefor we used a factor analysis method for continuous data although the data was found to be moderately skewed. Moreover, item 1, 2, 5, 7, 14 and 21 were kept in the analysis despite inter-item correlations >0.75. Although the authors discussed these items for similar underlying constructs interpretations of all translated items were not tested in the target population.

Scores on both subscales provide insight in the severity of the pain-related disability in both daily routine activities as well as more physical vigorous activities. Clinicians could also use the DCALI to provide more tailored care specific to a domain with disability.

Next step in the validation of the DCALI is to asses other parts of the methodological quality of measurement instruments.[25] Besides reproducing the results of the EFA by a confirmatory analysis in other populations with chronic pain like recurrent abdominal pain or disease-related pain. Moreover, evaluating the face- and content validity would be valuable. Testing the interpretation of the items of the DCALI by the target population increases the usefulness in daily practice by clinicians. This might also provide an explanation for the items that changed subscale with the original CALI21-C. Furthermore, it is valuable to assess test-retest reliability and the sensitivity to changes of treatment or interventions to enable the measurement to be used as an evaluation in changed levels of activity limitations in research or as a response to treatment.

Conclusion

The Dutch version of the Child Activity and Limitation Interview demonstrated good internal consistency and aspects of construct validity in a sample of Dutch-speaking school-aged adolescents seeking help for chronic musculoskeletal pain who are comparable to the study sample. Therefor the DCALI can be used in adolescents with chronic musculoskeletal

pain comparable to this study sample to assess the presence and severity of pain-related disability in both daily routine activities and more physically vigorous activities in school-aged children and adolescents with chronic musculoskeletal pain complaints.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Supplementary Table S2.1. Frequency scores of individual items

		CALI.1	CALI.2	CALI.3	CALI.4	CALI.5	CALI.6	CALI.7	CALI.8	CALI.9	CALI.10	CALI.11
N	Valid	74	74	74	74	74	74	74	74	74	74	74
	Missing	0	0	0	0	0	0	0	0	0	0	0
Mean		1.93	2.81	0.65	1.30	2.80	2.08	1.24	0.47	1.54	2.20	1.64
Std. Error of Mean		0.153	0.159	0.113	0.155	0.150	0.157	0.129	0.073	0.135	0.175	0.166
Std. Deviation		1.317	1.372	0.971	1.332	1.293	1.352	1.108	0.624	1.161	1.508	1.429
Variance		1.735	1.882	0.943	1.773	1.671	1.829	1.228	0.390	1.348	2.273	2.043
Skewness		0.091	-0.925	1.411	0.719	-0.862	-0.117	0.430	0.973	0.601	-0.208	0.298
Std. Error of Skewness		0.279	0.279	0.279	0.279	0.279	0.279	0.279	0.279	0.279	0.279	0.279
Kurtosis		-1.015	-0.430	0.865	-0.652	-0.380	-1.085	-0.665	-0.060	-0.369	-1.329	-1.258
Std. Error of Kurtosis		0.552	0.552	0.552	0.552	0.552	0.552	0.552	0.552	0.552	0.552	0.552
Range		4	4	3	4	4	4	4	2	4	4	4
Minimum		0	0	0	0	0	0	0	0	0	0	0
Maximum		4	4	3	4	4	4	4	2	4	4	4
Likert % valid	**0**	17.6	10.8	60.8	37.8	8.1	17.6	33.8	59.5	17.6	21.6	31.1
	1	20.3	9.5	23.0	24.3	10.8	14.9	23.0	33.8	39.2	9.5	18.9
	2	29.7	10.8	6.8	17.6	13.5	28.4	31.1	6.8	23.0	25.7	18.9
	3	16.2	25.7	9.5	10.8	28.4	20.3	9.5	0.0	12.2	13.5	17.6
	4	16.2	43.2	0.0	9.5	39.2	18.9	2.7	0.0	8.1	29.7	13.5

Supplementary Table S2.1 continues on next page.

Supplementary Table S2.1. *Continued*

		CALI.12	CALI.13	CALI.14	CALI.15	CALI.16	CALI.17	CALI.18	CALI.19	CALI.20	CALI.21	
N	Valid	74	74	74	74	74	74	74	74	74	74	
	Missing	0	0	0	0	0	0	0	0	0	0	
Mean		1.43	1.65	2.89	1.70	0.24	0.59	1.35	1.69	2.05	2.19	
Std. Error of Mean		0.126	0.168	0.160	0.141	0.077	0.102	0.145	0.160	0.157	0.177	
Std. Deviation		1.086	1.447	1.381	1.213	0.658	0.750	1.243	1.374	1.354	1.523	
Variance		1.180	2.094	1.906	1.472	0.433	0.765	1.546	1.888	1.833	2.320	
Skewness		0.047	0.197	-1.117	0.219	2.956	1.154	0.790	0.194	0.036	-0.257	
Std. Error of Skewness		0.279	0.279	0.279	0.279	0.279	0.279	0.279	0.279	0.279	0.279	
Kurtosis		-1.276	-1.380	-0.065	-0.866	8.466	0.021	-0.255	-1.172	-1.169	-1.391	
Std. Error of Kurtosis		0.552	0.552	0.552	0.552	0.552	0.552	0.552	0.552	0.552	0.552	
Range		3	4	4	4	3	3	4	4	4	4	
Minimum		0	0	0	0	0	0	0	0	0	0	
Maximum		3	4	4	4	3	3	4	4	4	4	
												Cumulative
Likert % valid	**0**	25.7	33.8	12.2	18.9	85.1	63.5	28.4	28.4	14.9	23.0	30.96
	1	25.7	13.5	6.8	27.0	8.1	16.2	35.1	16.2	23.0	10.8	19.50
	2	28.4	18.9	6.8	27.0	4.1	17.6	18.9	25.7	24.3	17.6	19.12
	3	20.3	21.6	28.4	18.9	2.7	2.7	8.1	17.6	17.6	21.6	15.39
	4	0.0	12.2	45.9	8.1	0.0	0.0	9.5	12.2	20.3	27.0	15.06

Chapter 3

Generalized joint hypermobility and anxiety in adolescents and young adults, the impact on physical and psychosocial functioning

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Abstract

The purpose of this study was to study the association between the presence of generalized joint hypermobility (GJH) and anxiety within a non-clinical high performing group of adolescents and young adults. Second, to study the impact of GJH and/or anxiety on physical and psychosocial functioning, 168 adolescents and young adults (mean (SD) age 20 (2.9)) were screened. Joint (hyper)mobility, anxiety, and physical and psychosocial functioning were measured. In 48.8% of all high performing adolescents and young adults, GJH was present, whereas 60% had symptoms of anxiety. Linear models controlled for confounders showed that adolescents and young adults with GJH and anxiety had decreased workload (ß(95%CI) -0.43(-0.8 to -0.08), p-value 0.02), increased fatigue (ß(95%CI) 12.97(6.3–19.5), p-value <0.01), and a higher level of pain catastrophizing (ß(95%CI) 4.5(0.5–8.6), p-value 0.03). Adolescents and young adults with only anxiety had increased fatigue (ß(95%CI) 11(4.9–19.5). In adolescents and young adults with GJH alone, no impact on physical and psychosocial functioning was found. Adolescents and young adults with the combination of GJH and anxiety were significantly more impaired, showing decreased physical and psychosocial functioning with decreased workload, increased fatigue, and pain catastrophizing. Presence of GJH alone had no negative impact on physical and psychosocial functioning. This study confirms the association between GJH and anxiety, but especially emphasizes the disabling role of anxiety. Screening for anxiety is relevant in adolescents and young adults with GJH and might influence tailored interventions.

Introduction

Generalized joint hypermobility (GJH) is characterized by the ability to move beyond the "normal" limits of range of motion in multiple joints. GJH is not necessarily synonymous with complaints and could also be helpful to excel, for example, in sports like rhythmic gymnastics or dance, where GJH is highly prevalent.[1,2] The pressure to perform in elite sports can be overwhelming with a possible increase in risk of injury and psychological overload.[3] When GJH, as a non-symptomatic condition, is accompanied by chronic musculoskeletal pain and soft tissue injury, GJH is referred to as Joint Hypermobility Syndrome (JHS).[4] JHS shows similarities with the hypermobile type of Ehlers–Danlos syndrome (EDS-HT).[5] EDS-HT is described based on major criteria as GJH and skin involvement and minor criteria as chronic pain, recurrent dislocations, and a positive family history.[6] A revision of the clinical criteria of EDS in 2017 clarifies the diversity within hypermobility.[7] In EDS-HT, soft tissue frailty was added and is now referred to as hypermobile EDS (hEDS). The term Hypermobility Spectrum Disorder (G-HSD) is currently used for JHS and former EDS-HT patients who do not fulfill the new criteria (hEDS).[7]

There have been minimal studies pertaining to disease progression in GJH, h-EDS, and HSD, with the available studies primarily addressing physical functioning.[8,9] In the disease progression of hEDS/HSD from childhood, adolescence, and adulthood roughly three phases are proposed based on cross-sectional observations by Castori et al.[10] The first phase, in childhood and adolescence, is dominated by an excessive amplification of tissue laxity and increased joint flexibility, while in adulthood phases, two and three describe next to physical factors like GJH, and psychosocial complaints like pain avoidance, anxiety, and depression. Phases two and three seem to have an increasing impact on quality of life accompanied by physical deconditioning and limited joint mobility.[10] However, this theory has not been verified yet. Current models in the GJH literature describe an association between GJH and anxiety but do not differentiate individuals with both GJH and anxiety from those with GJH alone.[9,11] The association between GJH and anxiety and the impact on physical functioning in healthy adolescents and young adults has not been studied in detail, whereas adolescents and young adults, in this specific lifespan, might be even more vulnerable for anxiety related disability, based on fear of negative evaluation or social phobias.[12] The impact might best be studied in a population in which hypermobility is highly prevalent with 57%, such as in young high performing dancers.[1,2] Hypermobility is common in high performance dancers because it is perceived as a sign of talent.[13]

Our objective is to study the impact of GJH and anxiety on physical and psychosocial functioning within a non-clinical group of high performing adolescents and young adults.

Materials and methods

Two cohorts of first year students of a dance academy were screened on musculoskeletal complaints, and physical and psychosocial functioning a week before the start of their education in August 2015 and 2016. All students were enrolled after they successfully completed the regular selection and audition procedure. Students were eligible for inclusion when (1) no orthopedic, cardiopulmonary, rheumatological, or neurological conditions or disorders influencing physical performance were present, and (2) they were able to understand the questionnaires and to adhere to the protocol.

From all participants, written informed consent was obtained. To create an open and safe environment, the screening took place outside the dance academy in the outpatient clinic of a university medical center without presence of staff of the dance academy. The outcomes were shared individually with the student without informing the dance academy, in order to secure the privacy. The study was approved by the Medical Ethical Committee of the Amsterdam University Medical Center (reference numbers W15_093#15.0110 and W16_237#16.277).

Physiotherapy students performed the functional testing as assessors after having received intensive training. For three weeks, training of standardized operating procedures was performed by expert researchers with broad experience in screening GJH, and measurements were analyzed for inter-rater reliability. The expert researchers remained present during the measurements. In between, while resting, the questionnaires were filled in.

Demographic and body characteristics

Data regarding age, gender, medication use, and injury history were obtained. Body characteristics such as standing height (cm), measured with a wall mounted stadiometer, and weight (kg), measured by a scale both measured without shoes and heavy clothing (rounded to the nearest centimeter and 0.1 kg) were collected, and BMI was calculated (kg/m^2).

Physical functioning

Participants were asked if they suffered from a present injury or an injury in the past two weeks, which body part was affected, if it was traumatic, the duration, and if this was a recurrent injury. An injury was defined as “any physical complaint that enables you to participate in dance activities”.[14]

Joint (hyper)mobility The Beighton score (BS) to measure the presence of local and generalized joint (hyper)mobility was performed as the first assessment of the measurement set not allowing the participants to have a warming-up phase. The BS consists of five clinical bilateral maneuvers of the little finger, thumb, elbow, and knee, each side scoring 1 point, and the spine also scoring 1 point, resulting in a total score of 9 points. Generalized joint hypermobility (GJH) was determined by a Beighton score ≥5, as described by Juul-Kristensen et al. The Beighton score is a validated instrument to measure hypermobility in adolescents and adults with an acceptable inter-rater reliability.[15]

Muscle strength was measured by a hand-held dynamometer (Citec, Groningen, The Netherlands) according to a standardized protocol[16] and expressed in Newtons. Total muscle strength was presented as a composite score of strength tests in the ankle dorsal flexors, knee extensors, hip flexors, shoulder abductors, elbow flexors, and handgrip. The break method was conducted in the hip flexors, ankle dorsal flexors, elbow flexors, and the shoulder abductors. Regarding grip strength and muscle strength of the knee extensors, the make method was used.[16,17] Measurements were performed bilaterally three times, whereas the highest value of both sides was summed up and divided by two to create a mean muscle strength per muscle group. Values were compared to the reference's values of adolescents.[16] The reliability of hand-held dynamometry in children, adolescents, and adults has been established with test–retest correlation coefficients ranging from 0.74 to 0.99.[16]

Workload was measured by the steep ramp test (SRT) and performed at a protocolled electronically braked cycle ergometer (Lode Corival CPet; Lode B.V. Groningen, the Netherlands). After three-minutes of warming-up at 25 Watt (W), the ramp protocol[18] applied 20 W/10 s resistance, and the participant was instructed to maintain a pedaling frequency of 60 to 80 revolutions per minute (rpm). Peak performance was defined as the point at which despite strong verbal encouragement, the pedaling frequency dropped below 60 rpm. The maximum wattage was normalized for weight and expressed as W/kg. The SRT is a reliable and valid exercise test in adolescents and adults.[18,19]

Psychosocial functioning and pain intensity

Anxiety and Depression were measured by the Hospital Anxiety and Depression Scale (HADS).[20] The self-reported questionnaire consists of two subscales (anxiety and depression), each consisting of 7 items rated on a 4-point Likert scale from 0 to 3, with higher scores indicating higher levels of anxiety or depressive state. A subscale score equal or above 8 in the general population is an indicator of symptoms of anxiety or symptoms of depression.[20] Subscales showed good internal consistency (HADS anxiety Chronbach's

α=0.83 (0.68–0.93); HADS depression (Chronbach's α=0.82 (0.67–0.90)) and good concurrent validity[20] in somatic (mostly cancer), psychiatric, primary care patients, and the general population, including both adults and adolescents.

Fatigue was quantified by the Checklist Individual Strength (CIS20),[21,22] a self-reported questionnaire consisting of 20 items rated on a 7-point Likert scale ranging from 1 to 7 with higher scores indicating higher levels of fatigue. Known cut-off for severe fatigue is a total score equal or above 40.[21] The CIS20 has a good internal consistency of the total scale (Chronbach's α=0.90) and good validity in multiple groups.[23]

Pain coping was defined by both pain catastrophizing, measured by the Pain Catastrophizing Scale (PCS),[24] and vigilance, measured by the Pain Vigilance and Awareness Questionnaire (PVAQ).[25] The PCS asks the participants to reflect on past painful experiences and to indicate the degree to which they experienced each of 13 thoughts or feelings when experiencing pain. The self-reported questionnaire consists of 13 items rated on a 5-point Likert scale with higher scores indicating higher levels of catastrophizing. The PCS comprises subscales for rumination (4 items), magnification (3 items), and helplessness (6 items). The PVAQ measures the participant's attention to pain itself and changes in pain. The self-reported questionnaire consists of 16 items, which are rated on a 6-point Likert scale with higher scores indicating higher levels of attention. Both the PCS and the PVAQ showed good internal consistency of the total scores (Chronbach's α=0.95 for PCS, Chronbach's α=0.94 for PVAQ).[24,25]

Data analysis

Distribution of the data was checked, and if normality was confirmed by Kolmogorov–Smirnov mean, standard deviations and range were presented, whereas skewed data were presented as median (50th percentile) and interquartile range (25th and 75th percentile), and nominal data was presented as number and percentage. Data of the two cohorts (2015 and 2016) were combined, since an independent *t*-test, Mann Whitney-U, or the chi-square test for every variable showed no significant differences in demographic variables. Descriptive statistics stratified for gender were used to present the clinical characteristics and physical and psychosocial functioning. To study the impact of GJH and anxiety on physical functioning, either separately or in combination, four subgroups were constructed: (1) adolescents and young adults without GJH and anxiety (no anxiety/no GJH), (2) adolescents and young adults with GJH alone (GJH), (3) adolescents and young adults with anxiety alone (anxiety), and (4) adolescents and young adults with increased presence of both GJH and anxiety (GJH and anxiety). Univariate analysis was performed by

comparing outcomes of physical and psychosocial parameters of adolescents and young adults without anxiety and without GJH and the other three groups. A Bonferroni test was used for multiple testing with a significance level of 1.67%. Differences between groups were expressed as mean difference (MD).

Linear regression was performed to study the impact of GJH and anxiety on physical and psychosocial functioning. Dependent variables consisted of physical factor workload, muscle strength, and psychosocial factors such as fatigue, pain coping, and vigilance. The four subgroups, adolescents and young adults with GJH, adolescents and young adults with anxiety, and adolescents and young adults with GJH and anxiety, were used as independent variables. As potential confounders, age, gender, and BMI were introduced. Data are expressed as regression coefficients, 95% confidence intervals, and r-square.

Results

All 170 participants from the cohorts 2015 and 2016 were invited to participate. Two students declined to participate, and consequently 168 participants were included (Table 3.1). GJH was present in 82 (48.8%) participants with higher prevalence in females than males (respectively 56.7% and 35.9%, $p<0.01$). In total, 16.7% participants suffered from an injury at the time of the screening. Sixty one percent of all participants (68.3% in female and 46.8% in male) showed symptoms of anxiety.

Table 3.2 shows univariate analysis of psychosocial and physical functioning in adolescents and young adults without GJH and anxiety compared to the scores of adolescents and young adults with GJH or anxiety or both GJH and anxiety. Adolescents and young adults with GJH scored comparable on physical and psychosocial factors to their peers without GJH and without anxiety.

Univariate analysis showed that adolescents and young adults with GJH and anxiety had significant higher scores on fatigue (MD(SE) 11(3.0); p-value <0.01), catastrophizing (MD(SE) 5(1.9); p-value 0.01), lower muscle strength (mean difference (MD(SE) -268(57.6); p-value <0.01), and workload (MD(SE) -0.5(0.17); p-value <0.01) than adolescents and young adults without GJH and anxiety. Adolescents and young adults with anxiety alone had significant higher scores on fatigue (MD(SE) 10(3.0); p-value <0.01).

Linear regression models can be found in Figure 3.1a–e with a R^2 ranging from 0.05 to 0.73, indicating that a low to relatively high proportion of the variance was explained by the variables.

Table 3.1. Characteristics of all participants (*N*=168) by gender

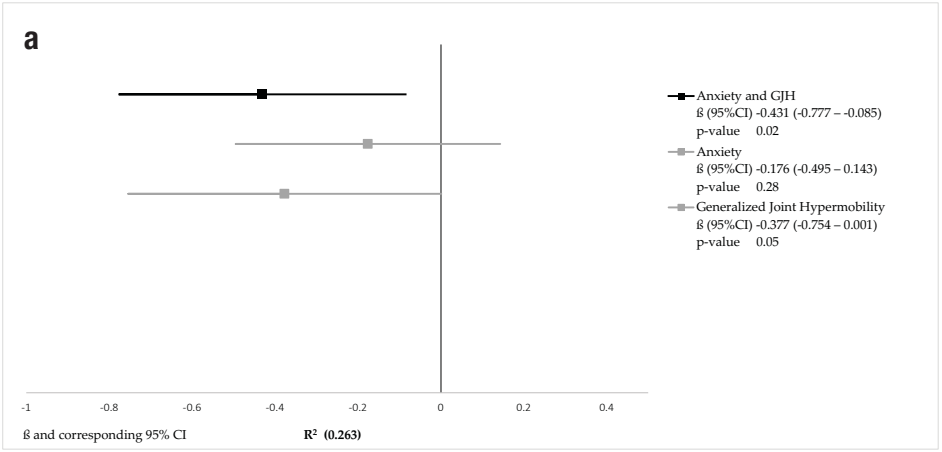
Group characteristics	All (*N*=168)						p-value
	Male (*N*=64)			Female (*N*=104)			
Physical factors							
Age (mean, SD, range)	20.4	(3.0)	16–29	19.7	(2.9)	15–29	0.12
Weight, kg (mean, SD, range)	67.8	(8.2)	54–91	57.4	(8.4)	39–100	<0.01*
Height, m (mean, SD, range)	1.78	(0.06)	1.65–1.91	1.66	(0.06)	1.48–1.85	<0.01*
BMI, kg/m^2 (mean, SD, range)	21.4	(2.0)	17.8–29.2	20.9	(2.7)	15.8–30.2	0.08
Beighton ≥5 (*N*, %)	23		36%	59		57%	<0.01
Wpeak (W/kg), (mean, SD, range)	6.0	(0.7)	4.4–7.5	5.2	(0.76)	2.45–7.24	<0.01*
Watt max, W, (mean, SD, range)	407	(56)	280–520	298	(57)	106–215	<0.01*
Strength, Newton, (mean, SD, range)	1843	(174)	1525–2263	1386	(170)	889–1699	<0.01*
Psychosocial factors							
Anxiety (median, 25th and 75th percentile)	8		1–14	9		0–14	0.06
Symptoms of Anxiety (*N*, %)	31		47%	72		68%	
Depression (median, 25th and 75th percentile)	3		0–14	4		0–10	0.80
Symptoms of Depression (*N*, %)	5		8%	6		6%	0.60
CIS 20 total score (median, 25th and 75th percentile)	50		23–89	52		20–89	0.60
Helplessness (median, 25th and 75th percentile)	5		0–15	4		0–15	0.31
Rumination (median, 25th and 75th percentile)	5		0–18	5		0–15	0.30
Magnification (median, 25th and 75th percentile)	3		0–10	3		0–10	0.24
Vigilance (median, 25th and 75th percentile)	37		7–60	37		12–58	0.78

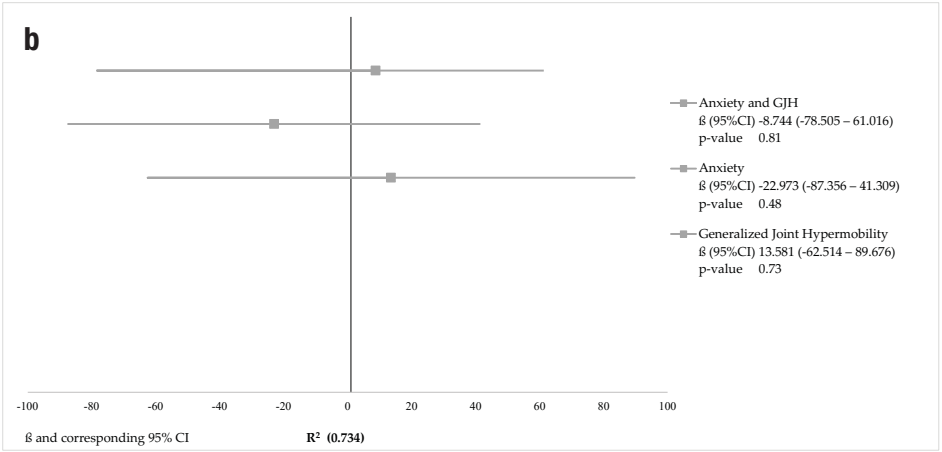
N, number of participants; BMI, body mass index; Wpeak, workload; Watt max, maximum wattage on the steep ramp test; CIS20, Checklist Individual Strength; PCS, Pain Catastrophizing Scale; SD, standard deviation; kg, kilogram; m, meter; %, percentage; W/kg, wattage per kilogram; P50 (25–75); * p-value <0.05.

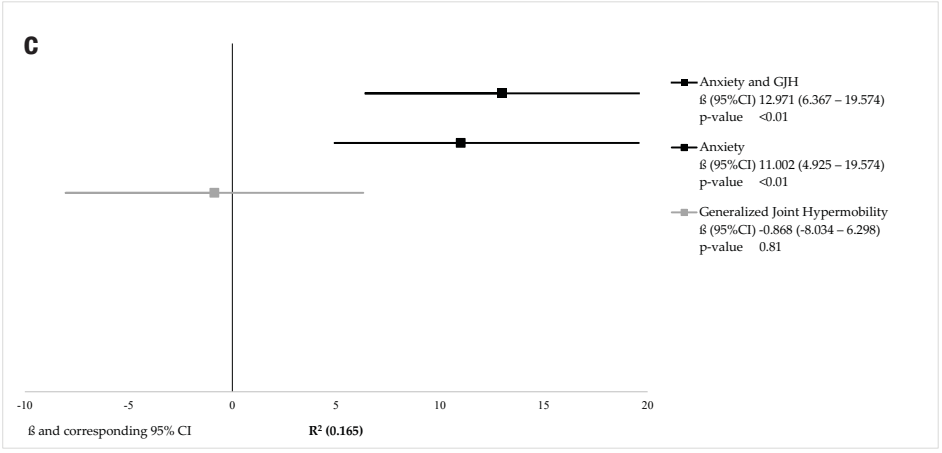
Table 3.2. Univariate analysis of scores on psychosocial and physical functioning in participants with anxiety and/or GJH and p-values compared to participants of the No GJH No Anxiety group (Bonferroni correction)

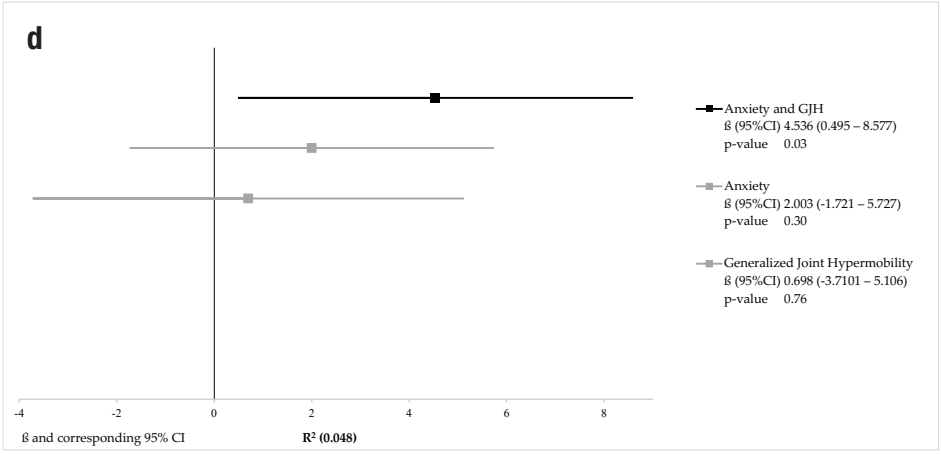
	No GJH no anxiety (*N*=38)		GJH (*N*=27)			Anxiety (*N*=48)			GJH and anxiety (*N*=55)			
												K-W
Variables					p-value			p-value			p-value	p-value
Age (mean, SD)	21.3	(3.4)	19.4	(2.1)	0.013	20.4	(2.9)	0.168	19.1	(2.6)	0.001*	<0.01*
Females (*N*, %)	16	42%	16	59%	0.173	28	58%	0.135	44	80%	<0.001*	<0.01*
Physical factors												
Weight, kg (mean, SD)	66.6	(11.4)	60.3	(8.9)	0.021	62.9	(7.9)	0.082	56.6	(7.6)	<0.001*	<0.01*
BMI, kg/m^2 (mean, SD)	22.3	(2.5)	20.8	(2.6)	0.021	21.6	(2.2)	0.190	19.7	(1.9)	<0.001*	<0.01*
Strength (mean, SD)	1701	(284)	1583	(250)	0.087	1582	(264)	0.047	1433	(257)	<0.001*	<0.01*
Wpeak (Wpeak/kg) (mean, SD)	5.8	(0.82)	5.4	(1.0)	0.098	5.6	(0.8)	0.168	5.3	(0.8)	0.002*	0.01
Psychosocial factors												
CIS 20 total score (median, 25th and 75th percentile)	46	23–73	46	25–62	0.462	57	21–89	0.001*	59	20–89	<0.001*	<0.01*
Vigilance (median, 25th and 75th percentile)	37	7–59	35	12–60		37	22–58		40	9–59		0.36
PCS (median, 25th and 75th percentile)	11	0–40	12	0–26	0.698	13	0–38	0.266	16	0–31	0.012*	0.03*

N, number of participants; BMI, body mass index; Wpeak, workload; CIS20, Checklist Individual Strength; PCS, Pain Catastrophizing Scale; SD, standard deviation; kg, kilogram; m, meter; %, percentage; W/kg, wattage per kilogram; P50 (25–75); K–W, Kruskal–Wallis to compare all groups; p-value display the difference with the reference group; No GJH, no anxiety; * p-value <0.0167.


a
Anxiety and GJH
ß (95%CI) -0.431 (-0.777 – -0.085)
p-value 0.02
Anxiety
ß (95%CI) -0.176 (-0.495 – 0.143)
p-value 0.28
Generalized Joint Hypermobility
ß (95%CI) -0.377 (-0.754 – 0.001)
p-value 0.05
-1 -0.8 -0.6 -0.4 -0.2 0 0.2 0.4
ß and corresponding 95% CI
R² (0.263)


b
Anxiety and GJH
ß (95%CI) -8.744 (-78.505 – 61.016)
p-value 0.81
Anxiety
ß (95%CI) -22.973 (-87.356 – 41.309)
p-value 0.48
Generalized Joint Hypermobility
ß (95%CI) 13.581 (-62.514 – 89.676)
p-value 0.73
-100 -80 -60 -40 -20 0 20 40 60 80 100
ß and corresponding 95% CI
R² (0.734)


c
Anxiety and GJH
ß (95%CI) 12.971 (6.367 – 19.574)
p-value <0.01
Anxiety
ß (95%CI) 11.002 (4.925 – 19.574)
p-value <0.01
Generalized Joint Hypermobility
ß (95%CI) -0.868 (-8.034 – 6.298)
p-value 0.81
-10 -5 0 5 10 15 20
ß and corresponding 95% CI
R² (0.165)



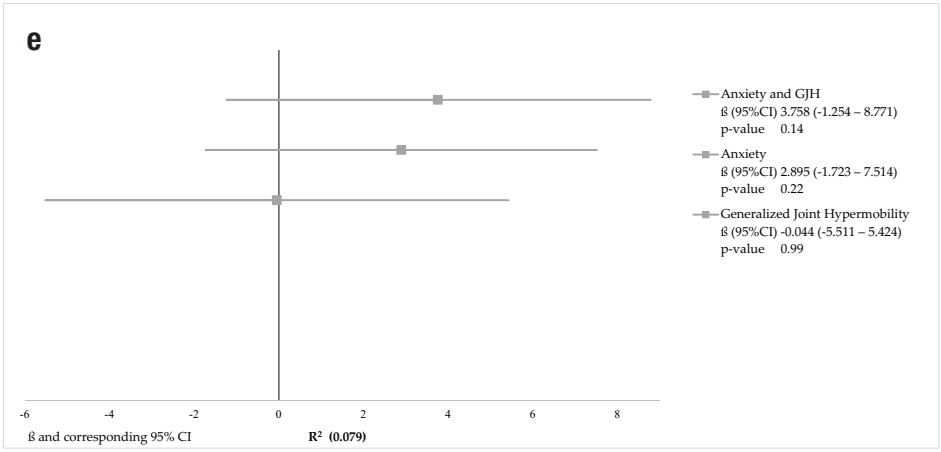


Figure 3.1. Linear regression models of physical and psychological factors adjusted for age, gender and BMI. **(a)** Workload (W/kg). Linear regression of factors associated with workload, adjusted for age, gender and BMI. **(b)** Muscle strength (N). Linear regression of factors associated with muscle strength, adjusted for age, gender and BMI. **(c)** Fatigue (points). Linear regression of factors associated with fatigue, adjusted for age, gender and BMI. **(d)** Pain catastrophizing (points). Linear regression of factors associated with pain catastrophizing, adjusted for age, gender and BMI. **(e)** Vigilance (points). Linear regression of factors associated with vigilance, adjusted for age, gender and BMI.

Linear regression models of psychological factors adjusted for age, gender, and BMI showed that adolescents and young adults with GJH and anxiety had increased scores of fatigue (ß(95%CI) 12.97(6.3–19.5); p-value <0.01) and pain catastrophizing (ß(95%CI) 4.5(0.5–8.6); p-value 0.03). Adolescents and young adults with anxiety alone also had increased levels of fatigue (ß(95%CI) 11.0(4.9–19.5); p-value <0.01), while adolescents and young adults with only GJH had no increased risk. Vigilance was associated with age

(ß(95%CI) 0.78(0.2–1.1); p-value 0.01) and BMI (ß(95%CI) -0.83(-1.6 to -0.1); p-value 0.03). Adolescents and young adults with either anxiety or GJH had no increased risk of maladaptive coping or vigilance.

Linear regression analyses regarding physical functioning after adjustment for age, gender, and BMI showed that adolescents and young adults with GJH and anxiety had a significantly decreased workload (ß(95%CI) -0.43(-0.8–0.08); p-value 0.02) (Figure 3.1). Adolescents and young adults with only GJH had no increased risk. After adjustment, GJH and anxiety, separately or combined, was not associated with muscle strength.

Discussion

Adolescents and young adults with the combination of GJH and anxiety had decreased workload and experienced more fatigue and pain catastrophizing. GJH alone did not impede adolescents and young adults in their physical and psychosocial functioning.

Current models in the GJH literature[11] describe an association between GJH and anxiety but do not differentiate individuals with both GJH and anxiety from those with only GJH. Our results show that the overall workload was high, representing the physical capacities of our sample as compared to the general population.[26] However, remarkably, within this group, differences existed; a decreased workload was found in adolescents and young adults with both GJH and anxiety compared to their peers without GJH and anxiety. Circumstances in this phase directly before the start of their new education can be perceived as highly demanding, especially by those vulnerable to anxiety related problems. Challenging expectations about their physical performance (potentially especially as perceived important by themselves) can trigger a negative impact of pre-existent psychosocial factors, such as uncertainty, anxiety, or fear. Presence of fear (f.e. fear of failure, fear of injury) and psychological stress in these high performers can induce fear avoidance behavior, which may have influenced maximal performance of individuals with GJH and anxiety. Performance avoidance goals were also observed by Lench et al. in participants with high trait anxiety,[27] and a recent review on hypermobile adolescents and young adults proposed that vulnerability to anxiety might cause avoidance behavior as a coping strategy to avoid injury and complaints.[9] In addition, GJH is highly prevalent in the general child population and considered common during growth.[28] Some adolescents develop primarily musculoskeletal complaints, and GJH is associated with functional disability.[29] The adolescents and young adults with GJH and anxiety in our sample did not experience disability; however, they were not able to perform physically equally to reference values.

Furthermore, the presence of increased experience of fatigue, anxiety, and pain catastrophizing in adolescents and young adults with GJH and anxiety compared to adolescents and young adults with anxiety alone who only showed increased experience of fatigue, could suggest that they might already have been struggling to keep up. This suggestion is supported by the literature with different types of anxiety disorders in adolescents showing that somatic symptoms are associated with anxiety severity and impairment in life.[30,31]

Within GJH and hEDS/HSD studies, the primary focuses are often on physical symptoms in order to explain physical functioning. Remarkably, we found in our study sample a high percentage of symptoms of anxiety that seems to impact physical functioning even more. The present study has several limitations. First, the external validity of our results: We included a sample of high performers (pre-professional dancers) due to their known high prevalence of GJH. They were selected on a high-performance level of physical and psychosocial functioning but have not started their education. Literature regarding Dutch high performers from the Netherlands Olympic Committee, Netherlands Sports Confederation describe a high incidence of symptoms of anxiety of 57%, comparable to the prevalence in our sample.[32]

It is tempting to relate anxiety to the risk of injury these adolescents and young adults might have. In the literature, this well-known concept is referred to as pain related fear and is frequently described in pain populations. The (interpersonal) fear avoidance model is expressing that fear could result in a vicious circle of a psychological trait causing avoidance and eventually could lead to de-conditioning.[33] Our findings also show that participants with anxiety but no hypermobility do have an increased level of fatigue but no pain catastrophizing nor decreased physical functioning. This suggests that the anxiety seems to contribute to a psychological component of fatigue but without restraints for physical capacity and coping in adolescents and young adults without hypermobility. Moreover, our sample is currently starting a professional dance education program, and therefore avoidance or disuse seems not evident within our sample at this specific timepoint based on their choice to participate in an educational program at a dance academy. However, it is possible that participants with GJH and anxiety did show avoidance within our measurements.

Secondly, the cross-sectional design and the specific timing of the measurement does not allow us to draw any conclusions about future dysfunction or potential drop-out. Follow up of these adolescents and young adults seems recommended.

Thirdly, all participants were healthy adolescents and young adults and, so far, successfully completed their audition and are waiting to start their education. Most of the individuals

with GJH mentioned within the screening that they were aware of their joint hypermobility, but none of the subjects was diagnosed with an anxiety disorder by a psychologist or psychiatrist. In our sample, the HADS was used to indicate an anxious state in a group of high performers in circumstances that can be perceived as high demanding and thereby stress provoking. These situations are normal to this population; however, the HADS is designed to indicate an anxious state, not to diagnose a psychiatric disorder.[34]

For external validation of our results, it is recommended to study the level of functioning in subjects with GJH alone compared to those with GJH and anxiety. To our knowledge, this has not yet been performed in healthy participants nor in participants with a clinical condition.

GJH and anxiety is found to decrease workload, increase levels of fatigue, and enhance pain catastrophizing. However, our results emphasize the importance of longitudinal studies to test whether the combined presence of GJH and anxiety could be used as a predictor for a dysfunctional trajectory or disease progression. Based on our result, we recommend that screening for anxiety is relevant in adolescents and young adults with GJH in high performers as well as in adolescents and young adults with G-HSD and h-EDS, since this might influence tailored interventions.

Conclusions

Adolescents and young adults with the combination of GJH and anxiety were significantly impaired, showing decreased physical and psychosocial functioning with decreased workload, increased fatigue, and pain catastrophizing. The presence of GJH alone had no negative impact on physical and psychosocial functioning. This study confirms the association between GJH and anxiety. Screening for anxiety is relevant in adolescents and young adults with GJH and might influence tailored interventions.

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Institutional review board statement

Ethical review and approval were waived for this study, due to being considered as not within the scope of medical research apart from the regular procedure (Waiver numbers W15_093#15.0110 and W16_237#16.277).

Informed consent statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data availability statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

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Conflicts of interest

The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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Chapter 4

Generalized joint hypermobility and anxiety are serious risk factors for dysfunctioning in dance students; A one-year follow-up study

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Abstract

Young professional dancers find themselves in a demanding environment. GJH within dancers is often seen as aesthetically beneficial and a sign of talent but was found to be potentially disabling. Moreover, high-performing adolescents and young adults (HPAA), in this specific lifespan, might be even more vulnerable to anxiety-related disability. Therefore, we examined the development of the association between the presence of Generalized Joint Hypermobility (GJH) and anxiety within HPAA with a one-year follow-up. In 52.3% of the HPAA, anxiety did not change significantly over time, whereas GJH was present in 28.7%. Fatigue increased significantly in all HPAA at one year follow-up (respectively, females MD (SD) 18(19), $p<0.001$ and males MD (SD) 9(19), $p<0.05$). A significantly lower odds ratio (ß(95%CI) 0.4(0.2–0.9); p-value 0.039) for participating in the second assessment was present in HPAA with GJH and anxiety with a 55% dropout rate after one year. This confirms the segregation between GJH combined with anxiety and GJH alone. The fatigue levels of all HPAA increased significantly over time to a serious risk for sick leave and work disability. This study confirms the association between GJH and anxiety but especially emphasizes the disabling role of anxiety. Screening for anxiety is relevant in HPAA with GJH and might influence tailored interventions.

Introduction

Young professional dancers find themselves in a highly demanding environment. As their future sporting career and life are determined by their current performance, these high-performing adolescents and young adults (HPAA) often complete extensive training hours.[1–3] With expectations and demands placed on the individuals by choreographers, teachers, parents, or themselves,[4,5] the pressure to perform in elite sports can be overwhelming, with a possible increase in the risk of injury and psychological overload.[6,7] Research within dance is primarily focused on causes of high injury risk. Self-reported seasonal prevalence of injury ranges from 40% (time-loss) to 92% (all health problems depending on the definition of injury).[8–10] However, two reviews that discuss the possible causes of injury point out that the methodological quality of the included studies is often lacking.[11,12] Factors identified with risk of injury include both physical and psychosocial factors. One of these physical factors is Generalized Joint Hypermobility (GJH), which is highly prevalent with 57% of young high-performing dancers.[13–15] Although this factor was found to be potentially disabling, GJH is within the dance community often seen as aesthetically beneficial and a sign of talent. Dance requires complex movements that often extend the normal range of joint movement. GJH can be helpful to excel in sports such as rhythmic gymnastics or dance but can also be accompanied by complaints. Patients with Joint Hypermobility Syndrome (JHS) or Ehlers Danlos syndrome hypermobility type (EDS-HT) show similar complaints such as chronic musculoskeletal pain end soft tissue injury but differ in others, such as skin involvement, positive family history, and recurrent dislocations.[16,17] The diversity within joint hypermobility is presented in the revision of the clinical criteria of EDS in 2017. Soft tissue frailty was added and is now referred to as hypermobile EDS (hEDS). For former EDS-HT patients who do not fulfill the new criteria and JHS patients, the term Hypermobility Spectrum Disorder (G-HSD) is currently used. In GJH, h-EDS, and HSD, disease progression has been barely studied over time and primarily addresses physical functioning.[18,19]

The GJH literature does not segregate individuals with GJH from individuals with both GJH and anxiety, although they underline the association between the two, anxiety and GJH.[19,20] Psychosocial complaints within the disease progression are proposed from adulthood based on cross-sectional observations by Castori et al.[21]

Recently, we found in a cross-sectional study that HPAA, a group of young professional dancers with the combination of GJH and anxiety, were showing significantly decreased physical and psychosocial functioning, illustrated by a decreased workload, increased

fatigue, and pain catastrophizing.[22] In a cross-sectional study, we confirmed the association between GJH and anxiety but especially emphasized the disabling role of anxiety. The presence of GJH alone had no negative impact on physical and psychosocial functioning.[22] High-performing adolescents and young adults in this specific lifespan might be even more vulnerable for anxiety-related disability based on fear of negative evaluation.[23]

The objective of our study is to examine the changes over time of impact of GJH and anxiety on physical and psychosocial functioning with a one-year follow-up within a non-clinical group of high-performing adolescents and young adults.

Materials and methods

The HPAA underwent a baseline measurement (T0) at the start of their education at a Dance Academy and a follow-up measurement exactly one year later (T1). This was performed the week before their educational program started. Students were eligible for inclusion when (a) no orthopedic, cardiopulmonary, rheumatological, or neurological problems influencing physical performance were present, and (b) they were able to understand the questionnaires and to adhere to the protocols. The measurements were performed by a team independent of the Dance Academy. Individual feedback on their performance was reported back directly to each student.

Data regarding (loss to) follow-up were collected for HPAA not participating in the follow-up measurement. Possible reasons for loss to follow-up were: (I) unable to participate due to training or logistic problems, (II) unwilling to participate, (III) proceeded their study at a different dance academy or participated in a guest program, and (IV) dropped out based on their performance or due to injury.

The studies were approved by the Medical Ethical Committee (reference numbers W15_093#15.0110 and W16_237#16.277), and written informed consent of all HPAA was obtained.

Procedures

After having received intensive training in the standardized operating procedures during three weeks by expert researchers with broad experience in screening GJH, physiotherapy students performed the functional testing as assessors, and their measurements were analyzed for inter-rater reliability. The assessors performed a specific measurement in both T0 and T1. The expert researchers (JdV, RE) supervised the measurements. The

screening performed at T1 was equal to the proceedings and measurements at the start of the study (T0). A detailed description of the measurements is described within the study of de Vries et al.[22]

In brief, measurements started with a visual analog scale combined with a Manikin to evaluate pain and questionnaires assessing injury history, fatigue, and general health status. HPAAs' joint hypermobility was measured without a warm-up using the Beighton score following completion of questionnaires.[24] Then body composition was measured, followed by muscle strength measurements using a hand-held dynamometer[25] and the Steep Ramp test performed at a standardized protocolled electronically braked cycle ergometer.[26] In between, questionnaires regarding psychosocial parameters of coping (by the Pain coping Scale and the Pain Vigilance and Awareness Questionnaire, PVAQ), anxiety, and depression (by the Hospital Anxiety and Depression Scale, HADS) were completed.[27–29]

Statistical analyses

The distribution of the data was checked and combined if normality was confirmed by a Shapiro–Wilk test and visual assessment. Data were presented as means, standard deviations, and ranges, whereas skewed data were presented as median (50th percentile) and range (25th and 75th percentile). Clinical characteristics were stratified for gender. Likewise, to the baseline study, the four subgroups based on GJH and anxiety were used within the analyses. Still, the classification of T0 was repeated at T1, and the results were compared to check for differences in classification with an intraclass correlation coefficient (absolute agreement). Afterward, differences in the baseline for physical and psychosocial parameters were compared between HPAA that participated in the follow-up and HPAA that did not (transferred students, dropped out, or were otherwise unable to participate at the measurements at T1). In order to study the impact of GJH and anxiety over time on those lost to follow-up, a log-linear regression was performed with the dependent variable participation in the second assessment (yes/no). The four subgroups were used as independent variables.

At T1, outcomes were compared between the reference group (HPAA without GJH and without anxiety) and the other three groups (based on the classification of T0) and to cut-offs from normative data (non-dancers). A Bonferroni test was used for multiple testing with a confidence level of 1.67%. Then, the four subgroups were tested on changes within each subgroup between T0 and T1 using a paired T-test or a Wilcoxon signed Rank test and presented as a mean difference (MD) with a standard deviation and a 95% confidence interval (95%CI).

Results

In total, 101 of the 168 HPAA screened at baseline (T0) participated in the follow-up measurements. Of the 46 HPAA that did not participate, 27 chose to proceed with their study at a different dance academy, 13 dropped out based on their performance, and 6 dropped out due to an injury. Twenty-two were unable to be present at the T1 measurement.

An overview at T1 with changes in physical and psychosocial parameters compared to T0 is presented in Table 4.1. GJH was present in 28.7% of all HPAA at T1 (33.3% of the females and 18.8% of the males). Anxiety did not change significantly over time and remained present in 52.3% of all HPAA (56.5% females and 43.8% males). Both male and female HPAA had a significant increase in total muscle strength (respectively, males MD (SD) 127 (169), $p<0.001$, females MD(SD) 55(213), $p<0.001$) and fatigue (respectively, males MD(SD) 9(19), $p<0.05$, females MD(SD) 18(19), $p<0.001$). Pain coping decreased significantly (respectively, males MD(SD) -5(9), $p<0.05$; females (MD)(SD) -4(8), $p<0.001$).

When comparing the subgroups at T0 and T1, there was an absolute agreement between the classification of GJH and anxiety at T0 and T1 was 54.7% ($p<0.01$).

We compared baseline characteristics of the HPAA who missed T1, dropped out, or transferred with the HPAA that were screened at T1. All HPAA that missed T1 had at T0 significantly higher psychosocial scores on anxiety MD(SD) 2(1), $p<0.01$, and vigilance MD(SD) 8(3), $p<0.01$ than their peers that were screened at T1. At baseline, the dropouts showed only significantly increased fatigue scores MD(SD) 9(3), $p<0.05$ than HPAA that were still enrolled at T1. Transferred students weighted significantly less MD(SD) 4.2(2), $p<0.05$ and had significantly lower BMI MD(SD) 2.2(0.5), $p<0.01$ at baseline than HPAA that were still enrolled at T1.

In order to study the impact of GJH and anxiety, the outcomes of physical and psychosocial parameters of the reference group (HPAA without GJH and anxiety) were cross-sectionally compared to the other three groups. The group with GJH and the group with anxiety scored comparable on physical and psychosocial factors to their peers without GJH and anxiety.

HPAA with GJH and anxiety weighted significantly less (respectively, MD(SD) p-value 8.6(2.9), $p<0.05$) and had less muscle strength (respectively, MD(SD) p-value 195(201), $p<0.05$) as the reference group but also had almost twice as many females (84.0%).

Within each subgroup, changes in scores (delta) between T0 and T1 were calculated and presented in Table 4.2.

Table 4.1. Clinical characteristics at T0, T1 and difference scores for all dancers that were assessed at both measurements

	Males (N[a]=32)						Females (N=69)					
	T0		T1		Difference MD (SD) 95%CI[b]		T0		T1		Difference MD (SD) 95%CI	
Clinical characteristics												
Age	20 (3)	16 – 28	21 (3)	17 – 28	0.5 (0.4)	0.3 – 0.6	19 (3)	16 -30	20 (3)	16 – 30	0.4 (0.9)	0.2 – 0.6
Weight, kg[c] (mean, SD, range)	67.8 (7.9)	54 – 91	71.4 (8.4)	58 – 95	2.4** (3.5)	1.1 – 3.7	57.3 (8.4)	39 – 100	59.7 (8.3)	46 – 100	1.1* (2.7)	0.5 – 1.8
BMI, kg/m2[d] (mean, SD, range)	21.3 (2.0)	18 – 29	22.4 (2.2)	15 – 19	0.7* (1.7)	0.1 – 1.3	20.9 (2.7)	16 – 30	21.9 (3.0)	17 – 34	0.5* (1.6)	0.1 – 0.9
Joint hypermobility: Beighton (median, 25th and 75th percentile)	3	0 – 7	2	0 – 7			5	0 – 9	3	0 – 9		
Beighton (*N*, %[e])	7	21.9%	6	18.8%			37	53.6%	23	33.3%		
Pain; VAS, mm (median, 25th and 75th percentile)	17	0 – 303	28	0 – 241			11	0 – 347	1	0 – 277		
Presence of an injury last year (*N*, %)	10	31.2%	13	40.6%			23	33.3%	15	21.7%		
Psychosocial characteristics												
Fatigue total score (median, 25th and 75th percentile)	51	23 – 89	58	27 – 86			50	21 – 89	75	26 – 95		
Anxiety (median, 25th and 75th percentile)	7	1 – 14	7	2 – 13			9	0 – 14	8	2 – 16		
Anxiety disorders (*N*, %)	15	46.9%	14	43.8%			42	60.9%	39	56.5%		
Depression (median, 25th and 75th percentile)	4	0 – 14	5	0 – 14			4	0 – 10	3	0 – 13		
Catastrophizing, PCS[f] total (median, 25th and 75th percentile)	11	0 – 40	11	0 – 26			11	0 – 38	7	0 – 35		
Vigilance, PVAQ[g] total (median, 25th and 75th percentile)	39	7 – 60	35	20 – 65			34	12 – 58	36	7 – 64		
Physical characteristics												
Workload, Wrpeak (W/kg[h]), (mean, SD, range)	6.0 (0.7)	4.4 – 7.5	6.2 (0.8)	5.1 – 7.9	0.2 (0.8)	-0.1 – 0.5	5.2 (0.8)	2.5 – 7.2	5.3 (1.1)	0 – 7	0.0 (1.1)	-0.3 – 0.3
Total muscle strength (Newton) (mean, SD, range)	1844 (174)	1525 – 2263	1977 (190)	1423 – 2426	130** (165)	71 – 190	1384 (170)	889 – 1699	1478 (247)	0 – 1932	59* (213)	8 – 110

*p<0.05; **p<0.001 p-values test differences within individuals in groups between T0 and T1.

[a] *N* Number of participants, [b] MD (SD) 95%CI Mean Difference (Standard Deviation) 95%Confidence Interval, [c] kg kilogram, [d] m meter, [e] % percentage, [f] PCS "Pain Catastrophizing Scale" total score 0 – 52, [g] PVAQ "Pain Vigilance and Awareness Questionnaire" total score 0 – 80, [h] Wrpeak (W/kg) peak workload in wattage per kilogram.

Table 4.2. Changes (delta) in psychosocial and physical outcomes between T0 and T1 scores within dancers with Generalized Joint Hypermobility and/or anxiety, or no GJH and anxiety presented as mean difference, standard deviation and 95% confidence interval

	All (*N*[a]=101)											
	None (*N*=25)			GJH (*N*=19)			Anxiety (*N*=32)			GJH and Anxiety (*N*=25)		
Weight, kg[b]	2.2*	(3.6)	1 – 4	1.1	(2.7)	0 – 2	1.4*	(2.8)	0.4 – 2.4	1.4*	(3.0)	0.2 – 2.7
BMI, kg/m^2[c]	0.8*	(1.4)	0 – 1	0.3	(1.9)	-1 – 1	0.9*	(1.7)	0 – 1	0.2	(1.4)	-0.4 – 0.8
Joint hypermobility, Beighton	0	(2)	-1 – 1	-2*	(2)	-3 – -1	0	(2)	-1 – 1	-1	(3)	-2 – 0
Pain, VAS, mm	5	(81)	-28 – 38	41*	(78)	3 – 79	-14	(78)	-42 – 15	15	(69)	-13 – 44
Psychosocial characteristics												
Fatigue, CIS20[d] total score	16*	(21)	-28 – 38	25*	(20)	16 – 35	12*	(18)	5 – 18	12*	(19)	5 – 20
Anxiety	0	(3)	-1 – 2	2*	(3)	0 – 4	-1	(3)	-2 – 0	0	(2)	-1 – 0
Depression	0	(2)	-1 – 1	0	(2)	-1 – 1	1	(3)	-1 – 2	-1	(4)	-2 – 1
Catastrophizing, PCS[e] total	-4*	(8)	-7 – 0	-2	(8)	-6 – 2	-3	(9)	-6 – 1	-3	(10)	-7 – 1
Vigilance PCS[e] total?	-1	(12)	-6 – 4	1	(10)	-4 – 6	-1	(9)	-4 – 3	2	(11)	-3 – 6
Physical characteristics												
Workload, Wrpeak[f], W/kg	-0.1	(0.9)	-0.5 – 0.2	0.1	(1.9)	-5.1 – 4.7	0	(0.7)	-0.3 – 0.2	0.3*	(0.6)	0.0 – 0.54
Total muscle strength, Newton	118**	(126)	66 – 170	-12	(368)	-1385 – 364	109**	(144)	57 – 160	81*	(125)	29 – 133

*p<0.05; **p<0.001 p-values test differences within individuals in groups between T0 and T1.

[a] *N* Number of participants, [b] kg kilogram, [c] m meter, [d] CIS 20 "Checklist Individual Strength" total score 20 – 140, [e] PCS "Pain Catastrophizing Scale" total score 0 – 52, [f] Wrpeak (W/kg) peak workload in wattage per kilogram.

No GJH/no anxiety

HPAA without GJH and anxiety showed increased muscle strength and fatigue (respectively, MD(SD) p-value 118(128), $p<0.01$ and MD(IQR) p-value 16(-28–38), $p<0.05$) between T0 and T1. All other physical and psychosocial parameters remained stable.

GJH

HPAA with GJH showed significantly decreased Beighton score (respectively, MD(IQR) p-value-2 (-3 to -1), $p<0.05$) and pain complaints (respectively, MD(SD) p-value 41(78), $p<0.05$), whereas fatigue increased (respectively, MD(IQR) p-value 25(16–35), $p<0.05$) between T0 and T1. All other physical and psychosocial parameters remained stable.

Anxiety

HPAA with anxiety had significantly increased scores of muscle strength and fatigue (respectively, MD(IQR) p-value 12(5–18), $p<0.05$ and MD(SD) p-value 109(144), $p<0.01$) between T0 and T1. All other physical and psychosocial parameters remained stable.

GJH and anxiety

HPAA with GJH and anxiety showed increased muscle strength (respectively, MD(SD) p-value 81(125), $p<0.05$), workload (respectively, MD(IQR) p-value 0.3(0–0.54), $p<0.05$) and fatigue (respectively, MD(IQR) p-value 12(5–20), $p<0.05$) between T0 and T1. All other physical and psychosocial parameters remained stable.

Lost to follow up

Loglinear regression analysis showed only within HPAA with GJH and anxiety a significantly lower odds ratio, respectively, ß(95%CI) p-value 0.4(0.2–0.9); p-value 0.039, on participating in the second assessment. Of all HPAA with GJH and anxiety measured at T0, 55% dropped out before their second year started.

The other groups, HPAA without GJH and anxiety, GJH, and anxiety, showed lower dropout rates of respectively, 34%, 29%, and 33%, with no significant odds on participating in the second assessment.

Discussion

This follow-up study is the first to show the impact over time of GJH and anxiety in HPAA. Significantly more HPAA with the combination of GJH and anxiety at T0 were not seen at follow-up (T1). Of those HPAA that participated in T1 physical and psychosocial parameters were comparable to all HPAA, independent of the presence of GJH and/or anxiety. All HPAA had a significant increase in their level of fatigue between T0 and T1.

All HPAA that participated in the follow-up assessments showed that the presence of GJH and anxiety separately has no influence on their physical and psychosocial functioning.

However, a remarkable finding was the significantly higher loss to follow-up in the HPAA with both GJH and anxiety.[22] This is supported by the low odds of participation in the second assessment for the group with GJH and anxiety. This finding seems in accordance with earlier findings in the literature stating that HPAA with GJH is struggling to keep up, possibly resulting in more injuries and decreased levels of physical functioning.[13,30,31] However, these studies did not differentiate between individuals with GJH alone and individuals with the combination of GJH and anxiety.

In the present study, those with GJH alone had no increased risk of leaving the dance academy. The prevalence of anxiety in young athletes in the literature was only one-third of the prevalence we found using the same questionnaire. Known barriers to help-seeking for mental health in young athletes are described by Gulliver et al. and consist of not knowing about mental disorders or their symptoms, when to seek help, and being worried about what both the personal and sport environment around the high performer will think.[32]

It is important to mention that we conducted this research in a healthy, successful HPAA. All participants were informed about their scores, including the increased anxiety scores after the screening, in a personal report. Still, almost 80% that had anxiety at T0 remained anxious at T1, and HPAA with both GJH and anxiety decreased physical and psychosocial functioning at T0 compared to peers.[22] It is unknown if they reached out for help or consulted a professional for their mental problems, or changed their training routines after T0.

The overall increased fatigue scores were unexpected because the moment of measurement was just before the start of the academic year, after a six-week summer break. Moreover, 40% had a serious risk for sick leave and work disability at T1, again with a higher incidence in HPAA with GJH and anxiety. The demand for HPAA is high with general technical training and time spent to perfection the esthetic part of the performance. Dancers are found to

"dance through" their injuries and fatigue and value training and frequent repetition more than recovery time and rest.[33] When there is a negative balance between recovery time and training, HPAA could suffer from non-functional overreaching or overtraining syndrome.[34] Symptoms of overtraining syndrome and non-functional overreaching are characterized by fatigue, performance decline, and mood disturbances which could be a reason for quitting.

The presence of generalized joint hypermobility and psychosocial problems has recently been studied by Meulenbroek et al.[19] They stated that GJH seems to make individuals more vulnerable to injury and experience musculoskeletal pain more frequently. In addition, a vulnerability for heightened pain-related fear is proposed as an underlying mechanism explaining the relationship between GJH and disability. Thus far, the relation between anxiety and GJH or JHS/EDS has been mostly described within adults.[20,35–38] This is in accordance with a theoretical model of disease progression by Castori et al.[21,39] However, our study shows that not only in adults with GJH but already in adolescents and young adults with GJH, clinicians should be aware of the presence of anxiety.

This study has intrinsic limitations that need consideration. First, the T1 assessment took place right before the start of the second year at the dance academy. For HPAA that were not participating at T1, follow-up data were provided by the Dance academy. Students that missed the follow-up assessment but were eligible for starting did not share specific reasons for missing the assessment.

Dancers that chose to continue their dance education at a different dance academy did not share the underlying reasons or information if they continued at the same level or had to repeat the first year, for example. For these dancers that missed the assessment or continued elsewhere, it is not possible to draw any conclusions about their capacity to proceed with dance education. However, comparing the baseline characteristics of all loss to follow-up groups, it is shown that their physical functioning did not differ. The dancers that dropped out of the education might have been already struggling to keep up by having already increased fatigue levels at T0.

Secondly, we questioned the HPAA about their injury history and received treatment. Because this only concerned physical injuries and not their mental health, we do not have any information on whether they consulted a professional or adapted their routine in any way after receiving their personal report reflecting their scores of T0. Despite their awareness of their joint hypermobility, none mentioned a possible mental health issue. Therefore, it is unknown whether the high prevalence of anxiety is persistent due to not receiving help from professionals or not being effectively treated by professionals.

This study provides a clear insight into the physical and psychosocial parameters of HPAA in the starting phase of their dance education. It underlines the importance of a broader baseline screening, including both physical as well as mental aspects of the dancer. Clinicians working with dancers should realize that the combination of GJH with anxiety increases the risk of leaving the dance academy after one year and the presence of only GJH is no liability. Therefore, caregivers and staff should be sensitive to the presence of anxiety in dancers. Additionally, dancers should be informed about the possible consequences of "pushing through" and have access to a safe environment to discuss their anxiety.

Conclusions

We studied high-performing adolescents and young adults (HPAA) and the changes over time of impact of Generalized Joint Hypermobility and anxiety on physical and psychosocial functioning with one-year follow-up and found in 52.3% that anxiety did not change significantly over time, whereas GJH was present in 28.7%. Fatigue increased significantly in all HPAA at one-year follow-up. A significantly lower odds ratio for participating in the second assessment was present in HPAA with GJH and anxiety with a 55% dropout rate after one year. This confirms the segregation between GJH combined with anxiety or GJH alone. The fatigue levels of all HPAA increased significantly over time to a serious risk for sick leave and work disability. This study confirms the association between GJH and anxiety but especially emphasizes the disabling role of anxiety. Screening for anxiety is relevant in HPAA with GJH and might influence tailored interventions.

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Institutional review board statement

Ethical review and approval were waived for this study due to being considered as not within the scope of medical research apart from the regular procedure (waiver numbers W15_093#15.0110 and W16_237#16.277).

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Data availability statement

The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

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Conflicts of interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Chapter 5

Role of anxiety in individuals with generalized joint hypermobility: A systematic review

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Abstract

Objective: To present an overview of the existing knowledge of the presence of anxiety in individuals with generalized joint hypermobility (GJH) in different phases of their life.

Data sources: Medline, PsychINFO, and Cochrane were searched from inception to late August 2024.

Study selection: Observational studies that included participants aged >12 years with GJH without comorbidities and psychiatric conditions and provided any information regarding fear or anxiety symptoms.

Data extraction: Extracted data included study and population characteristics and data regarding anxiety and pain.

Data synthesis: Of the 532 identified articles, 32 were included, with a total number of 12,116 subjects. Most studies (*n*=24) included adults aged >21 years. In total, 11 studies included a population with asymptomatic GJH, and 21 included a sample with symptomatic GJH. Findings on the presence of anxiety were similar in all life phases in individuals with symptomatic GJH whereas in individuals with asymptomatic GJH, people in earlier life phases tended to report less anxiety. Pain complaints were highly frequent in populations with symptomatic GJH. Increased levels of anxiety seemed to be related to higher levels of hypermobility. The highest levels of anxiety were found in individuals with symptomatic GJH followed by those with asymptomatic GJH, who showed slightly increased (but not significant) different levels of anxiety than their peers without GJH.

Conclusions: Anxiety may be related to the different stages of the spectrum of GJH, in terms of severity. This review supports the need to screen for anxiety in individuals with GJH in all life phases independent of their complaints.

Introduction

Generalized joint hypermobility (GJH) involves excessive joint mobility. Prevalence ranges from 5–43%[1,2] in adults and 2–55%[3] in children and is influenced by factors such as sex, race, age, and assessment methods. In activities such as gymnastics and martial arts, GJH can be advantageous.[4,5] However, some individuals with GJH may experience musculoskeletal issues or systematic symptoms disabling them in daily life. GJH without complaints is considered the initial stage of joint hypermobility, with Ehlers-Danlos Syndrome (EDS), a hereditary connective tissue disorder, on the far end.

EDS comprises a group of hereditary connective tissue disorders marked by GJH, skin hyperlaxity, and tissue frailty affecting blood vessels, internal organs, joint and skin.[6] The latest international classification in 2017[7] encompasses 13 subtypes. This revision accommodated newly discovered gene mutations and provided a comprehensive clinical classification for the hypermobile type of EDS (hEDS). Diagnosis of hEDS remains primarily clinical due to unclear genetic underpinnings. Diagnostic criteria include GJH, signs of tissue fragility (e.g., mitral valve prolapse, mild skin hyperextensibility, pelvic floor prolapse, arachnodactyly), positive family history, and/ or musculoskeletal symptoms (e.g., pain, dislocations, joint instability). Exclusion of other EDS types, connective tissue disorders, or conditions causing GJH is essential.[7] When GJH is symptomatic but does not meet syndrome criteria, it is termed hypermobility spectrum disorder (HSD).[8]

Individuals with hEDS often experience reduced physical functioning in daily life.[9-11] Common musculoskeletal pain in both HSD and hEDS can lead to disability, driven by pain-related fear and anxiety.[9,12] Many attribute their decreased activity levels to pain, and fear of pain is particularly pronounced in those with chronic musculoskeletal issues.[13-15] This fear can cause avoidance behaviors even in the absence of pain, creating a cycle of inactivity and disability, as described in the Fear-Avoidance Model.[16-18] Misinterpreted pain signals can lead to fear and avoidance of activities that might worsen pain. The Fear-Avoidance Model has been adapted for HSD and hEDS, highlighting the added challenges of hypermobility, which increase injury risk and exacerbate this cycle.[19]

Anxiety is closely linked to quality of life across various populations. Reduced quality of life is a predictor of mental health issues, including anxiety disorders.[20] Anxiety experiences can differ by age; younger adults often feel shame or guilt, while older adults may experience fear.[21]

During adolescence, anxiety and chronic pain become more prevalent.[22] It is unclear if the effects of fear and anxiety in GJH change with age. Some articles suggest that while pain-related fear contributes to disability in adults with HSD, it may not affect younger individuals similarly.[23,24] Recent research indicates that, in adolescents, chronic pain – not GJH – may be the primary driver of fear and disability.[25]

In the past decade, there has been increasing interest in understanding how anxiety impacts individuals with diverse types of GJH, with or without associated complaints, and across various stages of life. Therefore, the aim of this review is to present a systematic analysis of the current knowledge on the presence of anxiety and pain in individuals with GJH, considering variations across life stages.

Methods

Search strategy and selection process

For the structure of this study, the PRISMA statement for Reporting Systematic Reviews[25] was used based on the published literature. The search strategy was built around the DDO (domain, determinant, outcome) format with "domain" being any individual aged >12 years, "determinant" being the presence of GJH in any form, and "outcome" being any data regarding anxiety or fear. The full search strategy is included in the appendix.

A literature search was conducted in the electronic databases Medline, PsychINFO, and Cochrane from inception until late August 2024. The search was created by all authors and first designed in Medline (PubMed) whereafter it was adapted to run in PsychINFO (EBSCO) and Cochrane. Databases were searched for articles published in English by the search strategy (Supplemental Appendix S5.1 "Search strategy", available online only at http://www.archives-pmr.org/).

The screening and selection process was performed through Covidence[a] and considered 3 phases. First, duplicates were removed. Second, 2 reviewers (J.v.D. and E.R.) performed an initial screening using study titles and abstracts. Possible disagreements were settled by a third reviewer (M.G.). Third, after reading the full text of the articles, the final selection was made. Eligibility criteria were articles that included participants who were ≥12 years old with GJH without other comorbidities affecting their functional status, without psychiatric conditions, and provided any information regarding fear or anxiety symptoms. Articles that studied psychiatric conditions, did not use an observational study design, or were not published or available in English were excluded.

Methodological quality

The integrity of the included studies was appraised critically using the critical appraisal tools of the Johanna Briggs Institute checklist for case-control[b] and cross-sectional[b] designs and the Critical Appraisal Skills Programme cohort studies checklist.[26,c] The tool was chosen accordingly to the research design. The Johanna Briggs Institute checklist for cross-sectional and case-control studies consisted of 8 and 10 items with answers of "yes", "no", and "unclear", and the Critical Appraisal Skills Programme cohort study checklist consist of 12 items with responses of "yes", "no", and "can't tell". To create consistency, critical appraisal responses "unclear" and "can't tell" were labeled as "unclear". Appraisal items included setting, study population, procedure, measurement issues, and analysis. Appraisal was performed by the first author (J.v.D.) and the fifth author (S.R.).

Data extraction and analysis

Because of significant heterogeneity of the selected studies in outcomes, diversity in the use of clinimetrics, and different cutoffs in assessing GJH, meta-analysis could not be performed. Data were analyzed descriptively. Descriptive characteristics (first author and year, study design, population, sex, age, main outcome of anxiety, and secondary outcome of pain) are described in a standardized summary of findings table. Data was collected by the first author (J.v.D.) and checked by the second author (E.R.). Age was categorized into 2 groups: adolescents and young adults were aged 12–21 years and adults aged >21 years. Age boundaries were set according to Kaplan's definition of life stage with early adolescents starting at 12 years of age.[27]

Results

A total of 32 articles met the inclusion criteria and are included in this review.[25,28-58] Figure 5.1 describes the PRISMA flowchart of our literature search.

Figure 5.2 shows the methodological quality of the included studies. Apart from the mainly cross-sectional design, sometimes with a case-control format, most were well-performed and described. Most procedural unclarities were in studies that used a digital questionnaire and did not disclose how provided answers may have been influenced by parents or others related to the test subject. Strategies to deal with confounding factors were often not addressed.

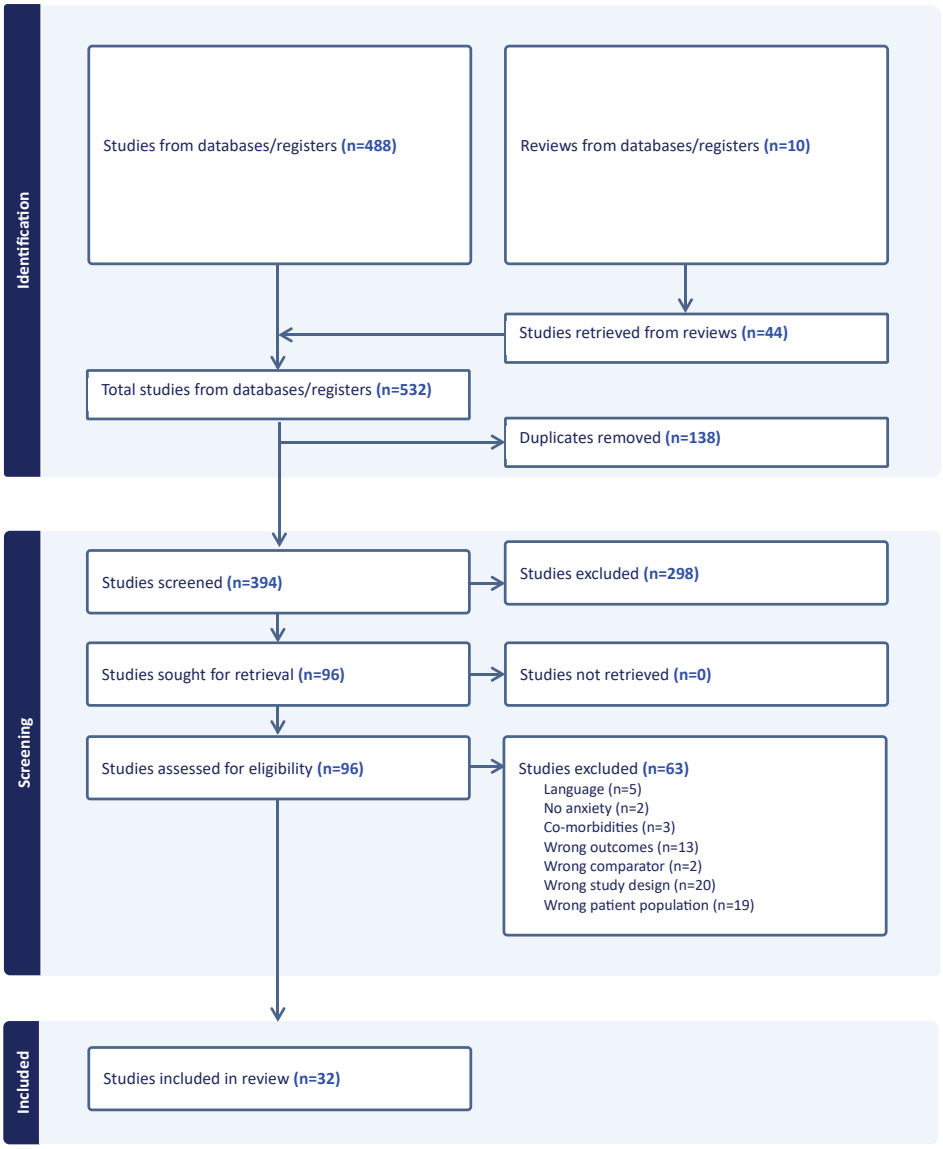

Figure 5.1. Flowchart of the identification of studies by databases.

The population characteristics of the studies are presented in Table 5.1. One study[41] included an only female sample; all other studies included both males and females. Eight studies[25,28,41,52,54,55-57] included adolescents and young adults between 12 and 21 years of age. Of these 8, 5 articles[28,41,52,54,56] included healthy participants with GJH without complaints, and 3[25,55,57] included patients with symptomatic GJH that were hEDS patients treated at a (university) medical center or a specialized hEDS clinic and an outpatient rehabilitation clinic.

Figure 5.2. Risk of bias

Cross-sectional	Baeza-velasco et al. 2011	Baeza-Velasco et al. 2018	Berglund et al. 2015	Bulbena et al. 1993	Bulbena et al. 2004	Bulbena et al. 2006	Bulbena et al. 2011	Bulbena-Cabré et al. 2018	Burón et al. 2018	Cellettì et al. 2013	de Wandele et al. 2014	Heidi et al. 2021	Johansen et al. 2020	Johansen et al. 2021	Liaghat ell al. 2022	Lumley et al. 1994	Murray et al. 2013	Nitermeyer et al. 2021	Palihez et al. 2011	Sanches et al. 2014	Tran et al. 2020	van Meulenbroek et al. 2017	van Meulenbroek et al 2021	Willich et al. 2023
1 Were the criteria for inclusion in the sample clearly defined?	U	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	U	Y	Y	Y	Y	Y	Y
2 Were the study subjects and the setting described in detail?	N	U	N	Y	Y	Y	Y	U	Y	U	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	U	Y	Y	Y
3 Was the exposure measured in a valid and reliable way?	Y	U	N	Y	Y	Y	U	Y	U	Y	Y	Y	Y	Y	Y	U	N	N	Y	Y	Y	Y	Y	U
4 Were objective, standard criteria used for measurement of the condition?	U	Y	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	N	U	Y	Y	Y	Y	Y	Y
5 Were confunding factors indentified?	Y	Y	U	Y	Y	N	N	U	Y	Y	Y	Y	Y	Y	U	U	N	Y	U	Y	Y	Y	Y	Y
6 Were strategies to deal with confounding factors stated?	N	U	N	U	U	N	N	N	Y	U	Y	N	Y	Y	N	U	N	N	U	Y	N	Y	Y	Y
7 Were the outcomes measured in a valid and reliable way?	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	U	U	U	U	Y	U	U	Y	Y	Y	Y	Y	Y	U
8 Was appropriate statistical analysis used?	Y	U	Y	Y	Y	Y	Y	Y	U	U	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y	Y

Figure 5.2 continues on next page.

Figure 5.2. *Continued*

	Case-control	Eccles et al. 2022	Ercolani et al. 2008	Gurer et al. 2010	Hakimi et al. 2023	Pasquini et al. 2014
1	Where the groups comparable other than the presence of disease in cases or the absence of disease in controls?	Y	Y	Y	Y	Y
2	Were cases and controls matched appropriatly?	U	Y	Y	Y	Y
3	Were the same cirteria used for identification of cases and controls?	U	U	Y	Y	U
4	Was exposure measured in a standard, valid and reliable way?	Y	Y	Y	Y	Y
5	Was exposure measured in the same way for cases and controls?	Y	Y	Y	Y	Y
6	Were confounding factors identified?	Y	Y	Y	Y	Y
7	Were strategies to deal with confounding factors stated?	Y	N	Y	N	N
8	Were outcomes assessed in a standard valid and reliable way for cases and controls?	Y	Y	Y	Y	U
9	Was the exposure period of interest long enough to be meaningful?	Y	Y	Y	Y	U
10	Was appropriate statistical analysis used?	Y	Y	N	Y	Y

	Longitudinal study	van Die-de Vries et al. 2022	Bathen et al. 2013	Chaleat-Valayer et al. 2019
1	Did the study adress a clearly focused issue?	Y	Y	Y
2	Was the cohort recruited in an acceptable way?	Y	U	U
3	Was the exposure accurately measured to minimise bias?	Y	Y	Y
4	Was the outcome accurately measured to minimise bias	Y	Y	Y
5	a) Have the authors identified all important confounding factors?	Y	N	N
5	b) Have they taken account of the condfouncing factors in the design and/or analysis?	N	U	N
6	a) Was the follow-up of subjects complete enough?	Y	Y	Y
6	b) Was the follow-up of subjects long enough?	Y	Y	Y

Y = Yes stated in the manuscript; N = No, not stated in the manuscript; U = Unclear description in the manuscript or Can't Tell wheter this has been done by the authors

Table 5.1. Study characteristics

Author	Design	Population	Hypermobility	Anxiety	Pain
Baeza-Velasco et al.[28] 2011	Cross-sectional	Undergraduate students (*N* 365) Age mean(SD) 21.1(2.1) years ♀ *N* 291, JHS *N* 130 (44.7%)	JHS Brighton criteria, greater or equal to 5	Liebowitz Social Anxiety Scale	Not reported
Baeza-Velasco et al.[29] 2018	Cross-sectional	Female hEDS outpatients (*N* 80) Age mean(SD) 37.1(11.5) years ♀ N 72 (90.0%)	hEDS Villefranche criteria	Hospital Anxiety and Depression Scale Tampa Scale of Kinesiofobia	Experiencing usual pain of severe/very severe intensity
Bathen et al. [30] 2013	Longitudinal	Female EDS-HT/JHS patients (*N* 12) Age median(range) 35(20– 51) years	Villefranche criteria and Brighton criteria	Tampa Scale of Kinesiofobia	Chronic pain
Berglund et al.[31] 2015	Cross-sectional	Adult EDS (*N* 250) Age mean(SD) 46(12) years ♀ *N* 223 (89%)	EDS Being member of the Swedish National Ehlers-Danlos Syndrome Association	Hospital Anxiety and Depression Scale	Back Pain, cervical, thoracic, lumbosacral or any back region.

Table 5.1 continues on next page.

Table 5.1. *Continued*

Author	Design	Population	Hypermobility	Anxiety	Pain
Bulbena et al.[32] 1993	Cross-sectional	Rheumatology outpatient clinic patients (*N* 173) Age mean(SD) JHS 41.8(13.9) years, Controls 48.1(13.5) years JHS *N* 114 (65.9%) Controls *N* 59 (34.1%)	JHS Beighton's criteria equal or greater than 3 or equal or greater score than 5 Beighton's diagnostic scheme	Hamilton Anxiety Rating Scale	Not reported
Bulbena et al.[33] 2004	Cross-sectional	Workers (*N* 526) ♂ *N* 323, 61.4% Age mean(SD) 25.2(2.9) years ♀ *N* 203, 38.6% Age mean(SD) 25.6(3.2) years	JH Hospital del Mar criteria (cut-off 3/4 ♂, 4/5 ♀)	State-Trait Anxiety Inventory (STAI)	Not reported
Bulbena et al.[34] 2006	Cross-sectional	Adolescents and adults (*N* 1305) Age mean(SD) 43(18.2) years ♀ *N* 708 (54.3%), JHS *N* 141 (19.9%) ♂ *N* 597 (45.7%), JHS *N* 41 (6.9%)	JHS Beighton score equal or greater than 5	Fear Survey Schedule (FSS)	Not reported

Table 5.1. *Continued*

Author	Design	Population	Hypermobility	Anxiety	Pain
Bulbena et al.[35] 2011	Longitudinal	Adolescents between 16 and 20 years old (*N* 137) Age after 15 years follow-up; mean(SD) 31.9(2.4) years ♀ *N* 64 (46.7%), JHS 22 (34.4%)	JHS Brighton criteria, greater or equal to 5	Modified Wolpe Fear Scale State-Trait Anxiety Inventory (STAI) Liebowitz Social Anxiety Scale Anxiety Sensitivity Index (ASI)	Not reported
Bulbena-Cabré et al.[36] 2018	Cross-sectional	Older adults (*N* 108) Age mean(SD) ♂ 68.5 years, ♀ 67.4 years ♂ *N* 49 (45%) ♀ *N* 59 (55%)	JHS Hospital del Mar criteria (cut-off 2/3 ♂ and 3/4 ♀)	Modified Wolpe Fear Scale State-Trait Anxiety Inventory (STAI)	Not reported
Burón et al.[37] 2018	Cross-sectional	Adults with and without panic disorder (*N* 120) Panic Disorder *N* 60, JHS *N* 44 (73.3%) Age mean(SD) 35.6(8.2) years Healthy controls *N* 60, JHS *N* 19 (31.7%) Age mean(SD) 34.7(6.9) years ♀ *N* 86 (71.7%)	JHS Hospital del Mar criteria 3/4 for males 4/5 for females	Hospital Anxiety and Depression Scale	Not reported

Table 5.1 continues on next page.

Table 5.1. *Continued*

Author	Design	Population	Hypermobility	Anxiety	Pain
Celletti et al.[38] 2013	Cross-sectional	Adults with EDS-HT/JHS (*N* 42) Age mean(SD) 32.8(13.23) years ♀ *N* 40 (95.2%)	Villefranche criteria and Brighton criteria	Tampa Scale of Kinesiofobia	Type of pain: Chronica back pain, chronic arthralgias, chronic myalgias, chronic fatigues and recurrent headaches
Chaleat-Valayer et al.[39] 2019	Longitudinal	Adults with hEDS (N 19) and relatives (*N* 9) Age >18 years ♀ *N* 17 (89%)	hEDS Clinical diagnosis made by a physician	Hospital Anxiety and Depression Scale	Not reported
de Wandele et al.[40] 2014	Cross-sectional	Adults with EDS-HT cEDS vEDS Fibromyalgia controls (*N* 179) Age mean(SD) 32.3–47.6(8.76–14.35) years ♀ *N* 157	EDS Villefranche nosology	Hospital Anxiety and Depression Scale	Use of analgesics and opiates
Eccles et al.[41] 2022	Cross-sectional	Adolescents in the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort (N 3803) Age 14 and 18 years ♀ *N* 2097 (55.1%), GJH *N* 593 (28.3%)	GJH Beighton score greater or equal to 4	ICD-10 anxiety	Not reported

Table 5.1. *Continued*

Author	Design	Population	Hypermobility	Anxiety	Pain
Ercolani et al.[42] 2008	Cross-sectional	BJHS (*N* 30), Fibromyalgic (*N* 30) and controls (*N* 25) Asymptomatic adults with BJHS Age mean(SD) 32.3(10.4) years ♂ *N* 2 ♀ *N* 28 Fibromyalgic Age mean(SD) 32.2(9.4) years ♂ *N* 2 ♀ *N* 28 Controls (*N* 25) Age mean(SD) 33.9(39.3) years ♂ *N* 2 ♀ *N* 23	BJHS Beighton score equal or greater than 5	The symptom checklist 90-r	Not reported
Gurer et al.[43] 2010	Cross-sectional	Rheumatology Outpatient Clinic patients (*N* 94) JHS *N* 40 (42.6%) Age mean(SD) 41(12.8) years ♀ *N* 38 (95.0%) Control group *N* 54 (37.4%) Age mean(SD) 41(8.6) years ♀ *N* 47 (5.0%)	JHS Beighton score of at least 4	Hamilton Anxiety Rating Scale	Not reported

Table 5.1 continues on next page.

Table 5.1. *Continued*

Author	Design	Population	Hypermobility	Anxiety	Pain
Hakimi et al.[44] 2023	Longitudinal	Referred hEDS patients (*N* 25, 19 completed follow-up) Age mean(SD) 45(12) years ♀ *N* 18 (95%)	hEDS 2017 diagnostic criteria for hEDS	Hospital Anxiety and Depression Scale Tampa Scale of Kinesiofobia	Brief Pain Inventory
Heidi et al.[45] 2022	Cross-sectional	Adults with molecularly verified LDS or vEDS (*N* 52) Age mean(SD) 42.9(16.2), vEDS 42.1(18.7) ♀ *N* 30 (58.0%), vEDS *N* 11 (36.7%)	vEDS Verified vEDS registered at the TRS National Resource Centre for Rare Disorders in Norway	Hospital Anxiety and Depression Scale	Brief Pain inventory, NPRS and number of pain locations
Johansen et al.[46] 2020	Cross-sectional	Adults with molecularly verified LDS or vEDS (*N* 52) Age mean(SD) 42.9(16.2), vEDS 42.1(18.7) ♀ *N* 30 (58.0%), vEDS *N* 11 (36.7%)	vEDS Verified vEDS registered at the TRS National Resource Centre for Rare Disorders in Norway	Hospital Anxiety and Depression Scale	Presence of chronic musculoskeletal pain

Table 5.1. *Continued*

Author	Design	Population	Hypermobility	Anxiety	Pain
Johansen et al.[47] 2021	Cross-sectional	Adults with HTADs, molecularly verified LDS or vEDS Age median (quartiles (range) 43.5(31.5) 18–68 years, vEDS 38.5(35.3) 19–68 ♀ *N* 30 (58%), vEDS 11 (36.7%)	vEDS Verified vEDS registered at the TRS National Resource Centre for Rare Disorders in Norway	Hospital Anxiety and Depression Scale	Presence of musculoskeletal pain
Liaghat et al.[48] 2022	Cross-sectional	HSD or historical HSD with concomitant shoulder complaints for at least three months (*N* 100) Age mean(95%CI) 37.8(35.3–40.3) years ♀ *N* 79 (79%) Historical HD *N* 11 (11%) Generalized HSD *N* 89 (89%)	HSD Beighton (>= 5/9 for♀up to 50 years and >= 4/9 for those above 50 years and males without age-specific cutoffs) and 5PQ (>= 2/5)	Tampa Scale of Kinesiofobia	NPRS during the past 7 days
Lumley et al. [49]1999	Cross-sectional	Adults and Children with EDS or JHS (*N* 41) Age mean 39.6 years ♀ *N* 39 (95.1%)	Patients of a EDS clinic.	The symptom checklist 90-r	WHYMPI

Table 5.1 continues on next page.

Table 5.1. *Continued*

Author	Design	Population	Hypermobility	Anxiety	Pain
Murray et al. [50] 2013	Cross-sectional	Adult EDS-HT (*N* 466) Age >18 years ♀ *N* 419 (89.9%)	EDS-HT Selfreported to have a clinical EDS-HT diagnosis made by a physician	Hospital Anxiety and Depression Scale	McGill pain questionnaire
Niermeyer et al.[51] 2021	Cross-sectional	EDS+ specialty consultation (*N* 49) Age mean(SD) 28.4(10.4) years ♀ *N* 38 (77.6%)	EDS+ specialty consultation	Generalised Anxiety Disorder Assesment	MPI (3item 6point likert)
Pailhez et al.[52] 2011	Cross-sectional	Non clinical students (*N* 150) Age mean(SD) 16.5(0.6) years ♀ *N* 66, JHS 33 (39.3%)	EDS- type 3 Five part questionnaire for Identifying Hypermobility greater or equeal to 2	Fear Survey Schedule (FSS)	Not reported
Pasquini et al.[53] 2014	Cross-sectional	JHS/EDS-HT patients and controls (*N* 92) Age mean(SD) 32(12.7) years ♀ *N* 75 (81.5%), JHS/EDS-HT *N* 41 (54.6%)	JHS EDS-HT JHS by Brighton criteria EDS-HT Villefranche criteria	Hamilton Anxiety Rating Scale	Not reported

Table 5.1. *Continued*

Author	Design	Population	Hypermobility	Anxiety	Pain
Sanches et al.[54] 2014	Cross-sectional	University students (*N* 2300) Age mean(SD) 21(3.25) years ♀ *N* 1288 (56%), JHS *N* 561 (43.5%)	Joint Hypermobility Five part Questionnaire for Identifying Hypermobility greater or equal to 2	Back Anxiety Inventory (BAI)	Not reported
Tran et al.[55] 2020	Cross-sectional	Pediatric patients with hEDS (*N* 34) Age mean(SD) 14.7(2.9) years ♀ *N* 24 (71%)	hEDS Villefranche criteria	Pediatric Anxiety Symptoms and Depressive symptoms short form scales (PROMISS)	Most difficult complaint, presence of pain.
van Die-de Vries et al.[56] 2022	Longitudinal	High-performing adolescents and young adults (N 101) Age mean(SD) ♂ 20(3), ♀ 19(3) years	GJH Beighton score greater or equal than 5	Hospital Anxiety and Depression Scale	VAS

Table 5.1 continues on next page.

Table 5.1. *Continued*

Author	Design	Population	Hypermobility	Anxiety	Pain
van Meulenbroek et al.[25] 2017	Cross-sectional	Adolescents (N 116) Age mean(SD) HM 16(2.4) NHM 16.1(2.4) ♀ N 103 (88.8%), HM N 36 (35.0%) ♂ N 13 (11.2%), HM N 4 (30.8%)	GJH Beighton score equal or greater than 5	Pain Catastrophizing Scale for children	VAS
van Meulenbroek et al.[57] 2021	Cross-sectional	Adolescents with or without CMP and or GJH (N 920) Age mean(SD) 16.1–18.1(0.8–2.0) ♀ 74 (80.4%)	Beighton (>= 5/9 for adolescents older then 18 years, or >= 4/9 for adolescents younger then 18 years)	PHODA-youth	VAS
Willich et al.[58] 2023	Cross-sectional	Adults with cEDS or hEDS (N 259) Age mean(SD) 38.8(11) years ♀ 238 (91.9%)	cEDS or hEDS Selfreported to have a clinical diagnosis made by a physician	Depression Anxiety Stress Scale	Graded Chronic Pain Status

SD standard deviation; N number; IQR interquartile range; HM hypermobile; NHM not hypermobile; ♀ female; ♂ male; JHS joint hypermobility syndrome; BJHS Benign Joint Hypermobility Syndrome; hEDS hypermobile Ehlers Danlos syndrome; EDS Ehlers Danlos syndrome; EDS-HT Ehlers Danlos Syndrome the Hypermobility type; vEDS vascular Ehlers Danlos syndrome; cEDS classical Ehlers Danlos syndrome; HTAD hereditary Thoracic Aortic Disease

Twenty-two articles[29-33,34-40,42,43-49,51,53] included adults >21 years of age. Most of these studies presented participants <50 years of age, and only 1 study included older adults with a mean age of 68.5 years.[36] Six studies included a sample with asymptomatic GJH.[33-36,42,43] Fifteen studies[29-32,37-40,44-49,51,53] included patients with symptomatic GJH diagnosed with HSD/(h)EDS, with 4[29,38,49,51] recruiting patients from a specialized EDS unit, and 4 including known hEDS/HSD patients with no information if those individuals were currently receiving any medical care.

Two articles overlapped in age groups by including all adult patients with symptomatic GJH, hEDS >18 years.[50,58]

Two determine the presence of GJH at the time of the study, 10 studies used the Beighton score,[25,32,34,41-44,48,56,57] 6 the Villefranche criteria,[29,30,38,40,53,55] and 6 the Brighton criteria.[28,30,32,35,38,53] Five included only officially registered EDS patients[31,39,45-47] and 3 used the 5-part questionnaire.[48,52,54] In 4 studies, EDS patients were diagnosed by a physician or seen at a special EDS clinic[49,50,51,58] and 3 by the Hospital del Mar criteria.[33,36,37]

To assess anxiety and fear symptoms, the Anxiety Sensitivity Index,[29,41] Beck Anxiety Inventory,[54] Depression Anxiety Stress Scale,[58] Fear Survey Schedule (FSS),[34,52] Generalized Anxiety Disorder Assessment,[50,51] Hamilton Anxiety Rating Scale,[32,43,53] Hospital Anxiety and Depression Scale,[29,31,39,40,44-46,50,56] International Classification of Diseases, Tenth Revision anxiety,[41] Modified Wolpe Fear Scale,[35,36] Pediatric Anxiety Symptoms and Depressive symptoms short form scales,[25,55] State-Trait Anxiety Inventory,[33,35] and the Symptom Checklist-90-R[42,49] were used. In addition to the generic questionnaires, fear/anxiety-specific questionnaires were also used to assess kinesiophobia by the Tampa Scale of Kinesiophobia,[29,30,38,48] social anxiety by the Liebowitz Social Anxiety Scale[28,35,37] and the Social Phobia Inventory,[54] fears by the Fear Survey Schedule,[28,34,36,52] perceived harmfulness by the Photograph Series of Daily Activities – Youth,[57] and pain catastrophizing by the Pain Catastrophizing scale (for adults and for children).[25,29]

In total, 16 studies also collected data regarding pain[25,29-31,38,40,45-51,55-58] using the visual analog scale[25,56,57] or the Numeric Pain Rating Scale,[45,48] Graded Chronic Pain Status,[58] the McGill questionnaire,[50] the Multidimensional Pain Inventory,[49,51] the Brief Pain Inventory,[44,45] or an inventory of pain complaints in frequency[30,31,38,45-48,50,55] or use of medication as analgesics or opiates.[40]

Adolencents and adults with symptomatic GJH were diagnosed with either HSD[25,37,43,48,57] or hEDS[29,31,39,40,44,45-47,50,51,55,58] with 4 studies[30,38,49,53] including both HSD and hEDS criteria.

Within popualtions with symptomatich GJH, pain was highly frequent and often chronic, with mild to moderate intensity.[39,44-47,49-51,55,58] Two studies that included samples of all types of EDS and found that pain did not differ between the types.[49] However, 67.1% of adults patients with hEDS reported experiencing pain of severe to very severe intensity,[29] while in vascular EDS, adult patients presented no severe pain but only mild to moderate pain scores with an equal distribution of number of pain locations.[45] Types of pain in hEDS patients were described as chronic back pain (78.8%), chronic arthralgias/joint pain (83.3% of 99%), chronic myalgias (85.7%), and recurrent headaches (76.3%).[30,46]

An overview of associations between anxiety and GJH is presented in Table 5.2. Overall, anxiety was associated with GJH in almost all studies.

The role of anxiety in adolescents and young adults with asymptomatic GJH

Anxiety scores in adolescents and young adults with GJH without complaints were increased compared to peers without GJH.[28,41,54,56] Normal to mild social anxiety was present.[28,41,54]

The number of items that were indicated as fearful and the severity of the experienced fear and anxiety was significantly increased in adolescents and young adults with asymptomatic GJH compared to their peers without GJH.[52] High-performing adolescents with asymptomatic GJH and anxiety had fewer physical abilities and more pain and fatigue complaints than their peers without GJH and/or anxiety.[56] Pain was found to be significantly increased over time in high-performing adolescents with asymptomatic GJH without anxiety.[56]

Mild social anxiety was observed in undergraduate students with GJH but no complaints.[28] Another study highlighted the disabling impact of asymptomatic GJH coupled with anxiety. Specifically, in high-performing adolescents, researchers compared the disability levels among groups: those with both asymptomatic GJH and anxiety, those with only asymptomatic GJH, those with only anxiety, and those with neither GJH nor anxiety.[56] The study revealed that high-performing individuals with asymptomatic GJH and anxiety exhibited reduced physical abilities and more complaints over time than their peers. Additionally, anxiety levels remained high and stable over time.[56]

Table 5.2. Associations between anxiety and generalized joint hypermobility

Generalized anxiety						
Anxiety	Measurement	Association with GJH	Sample	Age mean	Author	Year
	ASI		A-symptomatic	18 years	Eccles et al.	2022
	Anxiety sensitivity	HSD > controls Females with GJH > control females				
	HADS		A-symptomatic	20 years	van Die-de Vries et al.	2021
	Clinical levels of anxiety	Anxiety was stable at 52.3%				
	HADS		A-symptomatic	21 years	Baeza-Velasco et al.	2011
	Anxiety	Females with GJH > control females				
	Clinical levels of anxiety	Females with GJH > control females				
	BAI		A-symptomatic	21 years	Sanches et al.	2014
	Anxiety	Females with GJH > Males with GJH				
	STAI		A-symptomatic	25 years	Bulbena et al.	2004
	State anxiety	HSD > controls				
	Trait anxiety	HSD > controls Male HSD > controle males Female HSD > controle males				
	ASI		A-symptomatic	32 years	Bulbena et al.	2011
	Anxiety sensitivity	no association				
	STAI		A-symptomatic	32 years	Bulbena et al.	2011
	State anxiety	HSD > controls				
	Trait anxiety	HSD > controls				
	SCL-90-R		A-symptomatic	32 years	Ercolani et al.	2008

Table 5.2 continues on next page.

Table 5.2. *Continued*

Anxiety	Measurement	Association with GJH	Sample	Age mean	Author	Year
	Anxiety	HSD > controls				
	HADS		A-symptomatic	35 years	Burón et al.	2018
	Anxiety	Panic disorder group (73.3% HSD) > control (31.7% HSD)				
	HAM-A		A-symptomatic	41 years	Gurer et al.	2010
	Severity of anxiety symptoms	HSD > controls				
	STAI		A-symptomatic	68 years	Bulbena-Cabré et al.	2017
	State anxiety	HSD > controls				
	Trait anxiety	HSD > controls				
	PROMIS Pediatric Anxiety Symptoms and Depressive Symptoms short form scales		Symptomatic	15 years	Tran et al.	2020
	Elevated anxiety (risk range)	29%				
	Clinically elevated anxiety	12% of the hEDS sample				
	DASS		Symptomatic	>18	Willich et al.	2023
	Anxiety	48.3% of the cEDS and 53.9% of the hEDS patients reported anxiety				
	HADS		Symptomatic	>18	Chaleat-Vayer et al.	2019
	Anxiety	Mean(SD) 10.8(4.1) in the hEDS sample				
	HADS		Symptomatic	>18	Murray et al.	2013
	Anxiety	73% of the hEDS sample reported anxiety				
	Severity of anxiety symptoms	HSD and hEDS > controls				

Table 5.2. *Continued*

Anxiety	Measurement	Association with GJH	Sample	Age mean	Author	Year
	PROMIS Pediatric Anxiety Symptoms and Depressive Symptoms short form scales		Symptomatic	15 years	Tran et al.	2020
	Elevated anxiety (risk range)	29%				
	Clinically elevated anxiety	12% of the hEDS sample				
	GAD		Symptomatic	28 years	Niermeyer et al.	2021
	Clinical levels of anxiety	49% of the EDS+ sample				
	HAM-A		Symptomatic	32 years	Pasquini et al.	2014
	Severity of anxiety symptoms	HSD and hEDS > controls				
	HADS		Symptomatic	37 years	Baeza-Velasco et al.	2018
	Clinical levels of anxiety	51.2% of the hEDS sample				
	HADS		Symptomatic	39 years	Johansen et al.	2021
	Clinical levels of anxiety	LSD > vEDS				
	SCL-90-R		Symptomatic	40 years	Lumley et al.	1999
	Anxiety	HSD and hEDS > other types of EDS				
	HADS		Symptomatic	42 years	Heidi et al.	2022
	Clinical levels of anxiety	LSD > vEDS				
	HADS		Symptomatic	42 years	Johansen et al.	2020
	Anxiety	no association				
	HAM-A		Symptomatic	43 years	Bulbena et al.	1993
	Severity of anxiety symptoms	HSD > controls				
	HADS		Symptomatic	45 years	Hakimi et al.	2023
	Anxiety	Mean(SD) score of the hEDS sample 9.8(4)				
	HADS		Symptomatic	46 years	Berglund et al.	2015
	Clinical levels of anxiety	74.8% of the EDS sample				

Table 5.2 continues on next page.

Table 5.2. *Continued*

Specific anxiety						
Fear of Pain	Measurement	Association with GJH		Age mean	Author	Year
	FOPQ-C		Symptomatic	16 years	van Meulenbroek et al.	2015
	Fear of Pain	Not associated				
Fear of Movement	Measurement	Association with GJH		Age mean	Author	Year
	Tampa Scale of Kinesiofobia		Symptomatic	33 years	Celletti et al	2013
	Fear of Movement	93% of the patiënt exceeded clinical cutoffs for activity avoidance and harm				
	Tampa Scale of Kinesiofobia		Symptomatic	35 years	Bathen et al.	2013
	Fear of Movement	HSD and hEDS median score 25				
	Tampa Scale of Kinesiofobia		Symptomatic	37 years	Baeza-Velasco et al.	2018
	Fear of Movement	similar scores in high- and low anxious HSD				
	Tampa Scale of Kinesiofobia		Symptomatic	38 years	Liaghat et al.	2022
	Fear of Movement	49% of the HSD patients exceeded clinical cutoffs for high dear				
	Tampa Scale of Kinesiofobia		Symptomatic	45 years	Hakimi et al.	2023
	Fear of Movement	Mean(SD) score of the hEDS sample 38.4(7.4)				

Table 5.2. *Continued*

Social Anxiety	Measurement	Association with GJH		Age mean	Author	Year
	Liebowitz Social Anxiety Scale		A-symptomatic	21 years	Baeza-Velasco et al.	2011
	Social anxiety	no association				
		78.8% of the HSD males scored a medium/high level of socialanxiety				
	Avoidance	Males with HSD > Males without HSD				
	Social Phobia inventory		A-symptomatic	21 years	Sanchez et al.	2014
	Social anxiety disorder	Females with HSD > Males with HSD				
	Liebowitz Social Anxiety Scale		A-symptomatic	32 years	Bulbena et al.	2011
	Social anxiety	HSD > controls				
	Liebowitz Social Anxiety Scale		Symptomatic	35 years	Burón et al.	2018
	Social anxiety	Panic diorder group (73% HSD) > controls (32% HSD)				
Specific Fears	**Measurement**	**Association with GJH**		**Age mean**	**Author**	**Year**
	FFS		A-symptomatic	16 years	Pailhez et al.	2011
	Intensity of fears	GJH > control				
	Frequency of fears	GJH > control				
	FFS		A-symptomatic	32 years	Bulbena et al.	2011
	Intensity of fears	Females with GJH > Males with GJH				
	Frequency of fears	not associated				

Table 5.2 continues on next page.

Table 5.2. *Continued*

Specific Fears	Measurement		Association with GJH		Age mean	Author	Year
	FFS			A-symptomatic	43 years	Bulbena et al.	2006
		Intensity of fears	Males with GJH > control males Females with GJH > control females				
		Frequency of fears	Males with GJH > control males Females with GJH > control females				
	MWFS			A-symptomatic	68 years	Bulbena-Cabre et al.	2018
			Not associated				

ASI Anxiety Sensitivity Index; HADS Hospital Anxiety and Depression Scale; GJH Generalized Joint Hypermobility; hEDS hypermobile Ehlers Danlos syndrome; HSD Hypermobile Spectrum Disorder; vEDS vascular Ehlers Danlos syndrome; LSD Loeys Dietz Syndrome; BAI Beck Anxiety Inventory; SCL-90-R the symptom checklist 90-revised; HAM-a Hamilton Anxiety Rating Scale Anxiety score; PROMIS Pediatric Anxiety Symptoms and Depressive Symptoms short form scales; GAD General Anxiety Disorder Assessment; FOPQ Fear of Pain Questionnaire; TSK Tampa Scale of Kinesiophobia; LSAS Liebowitz Social Anxiety Scale; FSS Fear Survey Schedule; MWFS Modified Wolpe Fear Scale; STAI State and Trait Anxiety Inventory.

The role of anxiety in adolescents and young adults with symptomatic GJH

Adolescents with symptomatic GJH aged 12–18 years had a moderate level of anxiety, with 12% of the patients scoring above the clinical cutoff[59] for elevated anxiety.[55]

Two studies included patients with chronic musculoskeletal pain (CMP) with and without GJH and healthy adolescents with and without GJH.[25,57] Elevated scores of perceived harmfulness in activities, as construct of pain-related fear, were experienced in adolescents with CMP compared to healthy peers; however, these scores were independent of the presence of GJH.[57] Also, the level of catastrophizing and pain intensity did not differ between adolescents with or without hypermobility and CMP.[25,57]

The role of anxiety in adults with asymptomatic GJH

Adults with asymptomatic GJH had higher anxiety scores[42,43] and more specific anxiety as state, trait anxiety, social anxiety, and severity of fears than controls without asymptomatic GJH.[33-36] Contradictory results were found on the frequency of fears in healthy adults with asymptomatic GJH compared to peers without asymptomatic GJH.[34,35] Psychological distress including anxiety was significantly higher within adults with asymptomatic GJH compared to healthy controls but did not exceed the cutoff for pathological levels of psychological distress including anxiety.[42]

The role of anxiety in adults with symptomatic GJH

Adults with symptomatic GJH had increased overall scores of anxieties[1,32,37,40,44,45-47,51,53] and kinesiophobia.[29,30,38,44,48] Psychological distress was increased but did not exceed pathological cutoffs.[49] In populations with symptomatic GJH, the presence of anxiety and pain complaints were accompanied by other psychosocial complaints such as pain catastrophizing, somatosensory amplification, and decreased social functioning.[29] Highly anxious hEDS patients scored significantly higher in pain catastrophizing and somatosensory amplification and lower in social functioning than those without high anxiety.[29]

Three studies that overlapped in age-groups by including all adult patients with symptomatic GJH, hEDS older than 18 years reported similar prevalences of anxiety[39,50,58] as the symptomatic groups.

Discussion

This systematic review studied the impact of anxiety/fear and pain in different types of GJH, in different life phases. With >60% of the included studies performed in the last decade, a growing interest has been shown in symptoms of anxiety/fear and pain in individuals with GJH.

The review showed that increased levels of anxiety seem to be related to the different stages in the spectrum of hypermobility, with more anxiety in individuals with symptomatic GJH compared to individuals with asymptomatic GJH and the general population. Although the levels of anxiety within adolescents and adults with asymptomatic GJH did not reach clinical levels, these scores were still significantly increased compared to those of the general population. Contradictory results were found on specific anxiety and fears in asymptomatic GJH, whereas increased scores of specific anxiety and fears were demonstrated in individuals with symptomatic GJH. Anxiety scores in clinical populations of individuals with symptomatic GJH seemed similar in different life phases. However, research in individuals with asymptomatic GJH tended to report fewer anxiety symptoms in earlier life phases.

In this review limited evidence was available regarding anxiety in adolescents with asymptomatic GJH, although in adolescents, anxiety is very common. About 28% of Dutch adolescents suffer from lifelong increased anxiety.[59,60] Although college students may be more prone to mental disorders as they are exposed to many stressors, they often do not seek help but prefer to deal with those problems alone or with friends and relatives.[61-63] This preference to avoid mental support is also found in adolescents with chronic pain and GJH who tend to focus on the physical nature of their pain and even downplay their levels of psychological distress and anxiety themselves when seeking medical help.[64] The limited focus in research on adolescents with asymptomatic GJH leaves a gap in understanding early psychological impacts.

The increased anxiety symptoms observed in adults with HSD and hEDS align with the anxiety seen in other chronic pain populations, including patients with rheumatoid arthritis.[65-68] While anxiety in adults with HSD and hEDS has been frequently studied, research on adolescents and young adults with GJH remains predominantly focused on the biological and physical consequences of the condition.[69,70] In contrast, other chronic pain populations recognize the role of psychosocial factors, such as anxiety and pain-related fear, in contributing to disability. This biopsychosocial approach acknowledges these factors as integral to understanding disability.[16,65,66,68,71,72] Consequently, the evaluation of psychosocial factors is incorporated into the diagnostic process for these populations.[73,74]

Research adopting a biopsychosocial approach is emerging, although it is still limited in this population.[75,76] In this review, such an approach was only applied to HSD and hEDS patients in specialized rehabilitation settings, where it is common practice to treat populations with complex disabilities. Rehabilitation is often necessary for children and adolescents with impairments and functional limitations, significantly impacting their functioning and well-being.[77] The referral of patients with complex disabilities to this type of care, based on their level of disability, may explain the higher presence of psychosocial factors in these populations. Recently, a framework has been presented to distinguish those with hypermobility as a common physical trait from those with more serious complaints or even hEDS.[78] In this framework, anxiety was not included as criteria but presented as a comorbidity factor in hypermobile children and adolescents and considered to be potentially distressing and disabling. If so, a different subtype in the framework is assigned.[78] Although this seems to acknowledge the role of anxiety in GJH, this is only concerning anxiety disorders.[78]

The results of this review underline the importance of understanding the full scope of impairment from GJH. It urges screening for anxiety in all types of GJH and being aware of the threshold of reporting these symptoms in adolescents and young adults.

Simultaneously, this overview of studies also show that the level of evidence of the included studies can still be improved, with only 3 longitudinal studies and further studies with a cross-sectional design. Methodological quality of the included studies showed that strategies in coping with confounding factors were often lacking, and descriptions of study procedures left room for improvement. Overall, the Beighton Score, as prescribed by the consensus statement of 2017, was the most used tool to determine GJH. Most studies examined adults and only a few studies focused on adolescents and young adults, especially within a clinical setting. Most of the included studies used generic questionnaires to explore anxiety symptoms. The variability in clinical measurements indicates that a standardized methodology for assessing anxiety in GJH populations has yet to be established. Although over half the studies also reported pain in addition to anxiety, only 1 studied pain in individuals with asymptomatic GJH.

Study limitations

There are some limitations that need to be considered. First, taxonomy was inconsistent even in studies published after the consensus statement of 2017.[7] In the original studies, historical terms were used such as joint hypermobility syndrome, benign joint hypermobility syndrome, hEDS, EDS, HSD, and EDS-hypermobility type. Heterogeneity in definitions of GJH and, accordingly, in diagnostic criteria and anxiety assessment tools reduced compa-

rability. To improve comparability, GJH was categorized into 2 groups: symptomatic and asymptomatic. Also, with most studies (*n*=27) having a cross-sectional design, associations between GJH and anxiety and pain do not establish causality. In 3 studies,[31,49,50] methodological quality was lacking; however, their findings were in line with the overall conclusions, and we decided to take their results into account as the intent of this review was to present the extent of the existing body of knowledge in the field of GJH and anxiety including all relevant studies. Due to the reliance in this review on cross-sectional studies, this review does not establish causality between GJH and anxiety. As a result, conclusions on the disabling influence of anxiety over time need to be made with caution. More longitudinal studies are needed to explore causal relationships between GJH and anxiety. Focus on psychosocial factors in younger populations with asymptomatic GJH is required to develop targeted interventions.

Conclusions

Anxiety levels vary across the spectrum of GJH. Individuals with GJH with complaints exhibit higher anxiety levels than those with asymptomatic GJH and the general population. While anxiety levels among adolescents and adults with asymptomatic GJH did not reach clinical levels, they are still significantly elevated compared to those of the general population. These findings underscore the importance of screening for anxiety in both symptomatic and asymptomatic individuals with GJH, across different age groups. Clinicians and support staff should be mindful of the barriers adolescents and young adults may face in expressing anxiety symptoms. Tailored treatment for symptomatic GJH should involve an interdisciplinary approach, focusing on both physical and psychosocial interventions.

Supplier

[a] Covidence; Veritas Health Innovation.

[b] JBI checklist for Case Control studies and JBI checklist for Cohort studies; Johanna Briggs Institute.

[c] CASP cohort study checklist; Critical Appraisal Skills Programme, UK.

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Data statements

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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Chapter 6

General discussion

The overall aim of this dissertation is to gain better insight into the nature, prevalence and associations of Generalized Joint Hypermobility (GJH) and anxiety, and the impact on daily functioning, societal and sport participation in adolescents and young adults.

In the introduction of this dissertation we met Anne, a 17-years-old girl with Generalized Joint Hypermobility (GJH) with occasional pain complaints in joints and soft tissues. She was about to start her professional dance career at the Academy of Theatre and Dance (ATD). We wondered how Anne was guided and educated with her GJH during her professional dance training and if there were possible functional- and psychosocial consequences to consider. We also questioned if trainers around Anne from the local dance school to the staff and lecturers of the ATD have sufficient knowledge about GJH and its (dis)advantages or risks. And perhaps most importantly when does her GJH shifts from being beneficial and asymptomatic towards becoming a disability with functional and societal consequences?

Let's first discuss Anne at the start of the educational program of the ATD, including her scores of the mandatory screening. Anne indicated that she sometimes suffers from pain in joints and soft tissues, rated average pain in the past 7 days 25 mm on a VAS scale (classified according to the domains of the International Classification of Function (ICF); *body function*) but without injury at that moment (ICF; *body function*). She was found to have Generalized Joint Hypermobility, rated 7/9 on a Beighton score with positive pink hyperextension both sides, positive thumb opposition left finger, positive elbow extension right arm, positive knee extension both sides, and positive score while bending forward in stance (ICF; *body function*). Muscle strength was within the normal range (ICF; *body function*) and workload was increased (ICF; *body function*). Anne screened positive on the presence of anxiety (HADS) (ICF; *personal factors*) and was found to have increased fatigue (CIS20) (ICF; *body function, activities*).

Despite her extra training efforts Anne experienced that her peers are as thin, strong and driven and as motivated as herself (ICF; *personal factors*). This slightly worries Anne. Her parents and friends are excited to see how well she will do in class (ICF; *environmental factors*). The extra training hours forced her to cancel several social activities with her friends (ICF; *participation*).

Based on these findings Anne was regarded to have asymptomatic GJH with anxiety and personality traits like perfectionism. Although she mentioned to be frequently fatigued, she was about to start "fresh" at the ATD after the summer break and looked forward to starting her new study.

Main findings

The main findings of this dissertation concern the role of anxiety in the development of symptoms and pain-related disability as well as societal participation in high-performing dancers (elite athletes) with asymptomatic GJH.

To assess pain-related disability linked to GJH, a new validated measurement tool was required. In Chapter 2, we examined the psychometric properties of the Dutch version of the Child Activity and Limitations Interview (DCALI). This questionnaire assesses pain-related disability in adolescents and possible outcomes of the impact of GJH and anxiety on daily life and societal participation. We found good internal consistency as well as excellent construct validity and therefor, the DCALI provides clinicians a valid tool for use in adolescents in Dutch rehabilitation care.

In Chapter 3 and 4, we first explored whether GJH and anxiety affected the physical- and psychosocial functioning in high-performing dancers. In this study with a cross-sectional design, we found that dancers with both GJH and anxiety experienced decreased physical and psychosocial functioning, reduced workload, increased fatigue and more pain catastrophizing compared to their peers. These findings were confirmed in a one-year follow-up study. In Chapter 5, we investigated systematically whether our findings regarding the presence of GJH and anxiety were in line with findings in other studies regarding the hypermobility spectrum such as Hypermobile Spectrum Disorder (HSD) or hypermobile Ehlers-Danlos Syndrome (hEDS). Therefore, we reviewed the existing literature of the full spectrum of joint hypermobility from (asymptomatic) GJH to Hereditary Connective Tissue Disorder (HCTD) for the role of anxiety. We found that anxiety may be related to the spectrum of joint hypermobility, with populations with HSD and hEDS were found to have the highest levels of anxiety compared to other populations with asymptomatic GJH.

Main findings in perspective

GJH and pain-related disability

The relationship between Generalized Joint Hypermobility (GJH) and the presence of disability is particularly complex in children and adolescents. In case of symptomatic GJH, hEDS has clear criteria.[1,2] However, symptomatic GJH that does not meet the criteria of hEDS, like HSD, may have a widespread and diverse symptom profile. Physical complaints in HSD are primarily reported in the musculoskeletal domain (young adults 95%, adolescents 85% and children 75%).[3] However, other physical signs including functional gastrointestinal

disorders, cardiovascular dysautonomia and other systemic involvement have been reported since.[2] Psychological characteristics in HSD like anxiety, depression and eating disorders were reported in literature in young adults and adolescents in respectively 25% and 10%.[3]

Given the wide-ranging impact on daily life and societal participation, it is important to understand how GJH-related complaints contribute to experienced disability.[1,2,4] Therefore, clinicians need effective tools to evaluate their impact. Disability due to pain seems a relevant construct in GJH as the prevalence of pain in GJH is reported to be highly increased.[2] Currently, there are only few instruments specifically designed to relate pain to experienced disability in this population, and moreover, none of these are available in Dutch. As a result, more generic measurement tools that include the construct of disability or combine disability with other components are commonly used, like Functional Disability Inventory (FDI) or the Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT), Pediatric Pain Disability Index and PROMIS Pain Interference Scale.[5–8] They do assess the difficulties in activities and participation but do not relate the perceived disability to the pain of the individual. Therefore, in Chapter 2 we examined the psychometric properties of the Dutch version of the Child Activity and Limitations Interview (DCALI). The CALI was originally developed to assess pain-related disability in adolescents.[9] Adolescents were asked about the activity limitations they experienced due to pain over the past four weeks. We found good internal consistency and excellent construct validity in a sample of adolescents with chronic pain, including adolescents with HSD and hEDS. This makes the DCALI suitable for use in adolescents in Dutch rehabilitation care.[115] With the DCALI's ability to measure the impact of chronic pain on activity- and participation levels in GJH, it is crucial to consider also the psychological factors that may contribute to the level of disability. The DCALI connects to biomedical- and psychosocial factors and may indicate pain in relation to disability in daily life. Presence of pain-related disability in adolescents with GJH (as assessed by the DCALI) may signal the need to further identifying the role of psychological factors such as fear and anxiety.

Pain-related fear

One of the identified triggers of pain-related disability is pain-related fear which can lead to altered movement patterns and eventually movement avoidance. The pathway of avoidance to disability is explained in the Fear Avoidance Model (FAM). This cognitive-behavioral framework starts with an initial pain experience and explains the development and persistence of chronic pain. Pain is highly frequent in individuals with GJH, as their joints are more susceptible to microtrauma, that may lead to the accumulation of slight

injuries over time.[4] Although microtrauma may initially go unnoticed, continuous exposure can trigger a persistent state of pain and discomfort.[4]

The FAM was recently adapted for adolescents with symptomatic GJH. Figure 6.1 includes the extra demand on the compensatory system for joint laxity to assure joint stability in GJH.[4,11,12] It addresses the micro-traumas that might occur as a consequence of joint instability leading to compensatory and altered movement patterns. These changes may result in overload in the musculoskeletal system.[11]

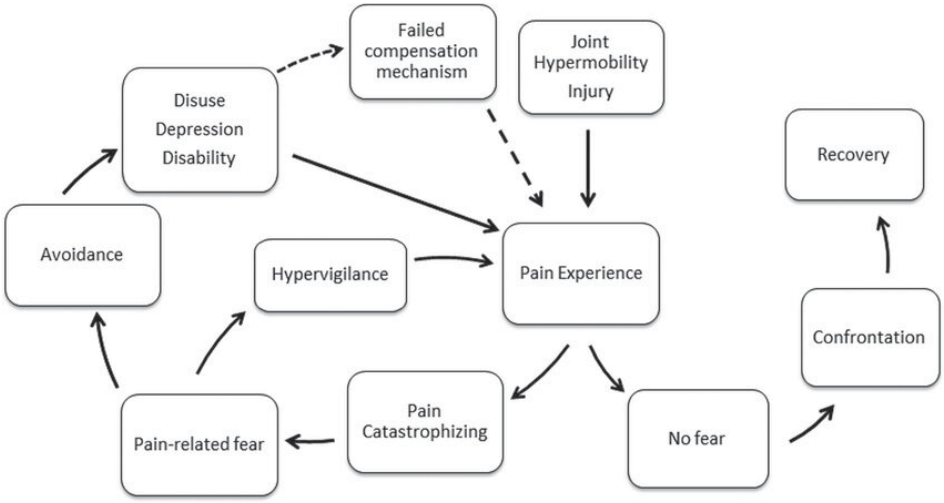

Figure 6.1. The applied fear avoidance model for adolescents with HSD / hEDS according to Van Meulenbroek et al. 2020.[11]

Asymptomatic and symptomatic GJH in adolescents

The psychological burden in adolescents with GJH has been acknowledged by including anxiety as a core comorbidity in the diagnostic framework that was developed during this thesis by an international group of pediatric experts and published by Tofts et al.[1] They proposed a "fluid" descriptive diagnosis allowing changes in presence of hypermobility, skin involvement, musculoskeletal complaints or core comorbidities.[1] In this framework symptoms may disappear, persist or increase over time enabling clinicians to differentiate between physiological, temporary joint hypermobility and underlying disorders in children and adolescents that have not yet reached biological maturity. GJH is referred to as asymptomatic in children and adolescents without the presence of musculoskeletal complaints linked to their hypermobility and core comorbidities, independent of the presence of skin

involvement. However, when combined with the presence of either musculoskeletal issues or core morbidities GJH is defined as symptomatic.[1] Core comorbidities included in the framework like anxiety could play a distressing or disabling role.[1] The framework uses clear diagnostic definitions and defines anxiety by the American Psychiatry Association DSM 5 for anxiety.[1]

Anxiety in high-performing adolescents with asymptomatic GJH

To examine the role of anxiety in adolescents with asymptomatic GJH, we studied a sample of high-performing adolescent dancers in Chapters 3 and 4. Participants were grouped based on the presence of GJH and/or anxiety. Those with both conditions experienced significant impairments in physical and psychosocial functioning, often leading to dropout from their education.

At baseline, dancers with GJH and increased anxiety exhibited decreased physical and psychosocial functioning as compared to their peers. Our longitudinal follow-up confirmed these findings, showing increased fatigue and dropout rates, that may indicate decreased physical and psychosocial functioning. In contrast, those with GJH but without anxiety maintained similar long-term functioning to their peers.

Dancers with GJH were prone to overload injuries and pain due to joint hypermobility and high workloads. When combined with pre-existing anxiety, this pain may lead to avoidance behaviours, as described by the Fear-Avoidance Model (FAM).[13]

Anxiety in athletes

Starting at the professional dance program with a disadvantage like presence of GJH and increased levels of anxiety compared to peers can be a result of the preliminary phase that often starts at a young age. The long and increasingly demanding journey towards a professional dance career may exacerbate musculoskeletal complaints associated with GJH, such as joint instability and the risk of injury, undermining its initial benefits.[13,14]

In elite sports, increased susceptibility to injury and risk-taking by too extensive training through pain, injury, and exhaustion are known consequences of a negative performance outcomes caused by the high physical and psychosocial demands placed on these athletes.[15–17] Other consequences include the pressure to perform, perfectionism, burn-out and overtraining and parental pressure or conflict.[18] As young athletes progress to becoming elite athletes, increased performance anxiety, increased fear of failure and increased performance expectations are experienced, ultimately resulting in lower self-confidence.[19,20]

In aesthetic sports such as dancing, performance is subjectively rated, which reduces the athlete's control over their evaluation.[21,22] This lack of control can be an extra dimension considering that young elite athletes often strive for perfection.[23] This perfection can enable them to surpass expectations, however in case of maladaptive perfectionism the fear of assessment by others may lead to burnout.[24,25] While literature states that in young elite athletes' anxiety symptoms rate similar to the general population,[21,26] whereas injuries or performance difficulties can lead to increased anxiety.[27] Dance is known for its competitive culture where dancers experience the pressure to perform and hide pain or injury or feel obliged to return to sport before being physically ready.[28,29] A possible explanation may be that young elite athletes might be more anxious about negative performance outcomes than about pain.

Anxiety in our high-performing sample with GJH may be multidimensional and consist of the fear of failure and negative performances outcomes as well as the fear of pain or reinjury due to their increased vulnerability from GJH.[23] Anxiety in our high-performing sample with GJH did not result in a behavioral response of movement avoidance. By choosing for a professional dance program, they may have exhibited coping strategies comparable to "over users," characterized by an endurance-related pain response (EPR).[30] This response includes thoughts of suppression, distraction, and minimizing pain, coupled with persistent task behavior despite severe pain.[12,30] Research studying coping mechanisms in high-performing adolescents with fear of failure showed that these adolescents often increased their training intensity in an attempt to avoid failure.[30,31] Consequently, unhealthy activity patterns are adopted, leading to overuse, exhaustion, pain exacerbation, negative moods, and periods of incapacity.[12,30] Although we did not focus on pain, we found similarly responses in the dancers with GJH and anxiety in Chapter 3 and 4. Their pressure to perform either placed upon them by themselves or their environment may have led to exhaustion and negative moods, particularly in those with increased fatigue scores at baseline, which may have caused dropout. Pain induced in dancers with GJH and anxiety may have triggered overuse like the EPR.[12,30] Following the endurance-related pain response to dysfunctioning leading towards disability and dropout.

The role of anxiety in GJH

In Chapter 5 we examined in detail the role of anxiety in GJH and reviewed the existing literature of the full spectrum of joint hypermobility from GJH to HSD and HTCD. Anxiety has shown its disabling role on the end of the spectrum in both adolescents and adults with HSD and HTCD. Higher levels of anxiety and psychological distress are often accompanied

by other psychosocial complaints such as pain catastrophizing, somatosensory amplification and decreased social functioning.[32–34]

Adolescents and adults with HSD and hEDS with pain-related disability often receive treatment or medical checkups in the primary health care and in case their situation is more complex, in rehabilitation centers and allied health professionals. In rehabilitation settings a biopsychosocial approach, that focusses both on the physical and psychosocial functioning often used to address complex health related disability.

Stigmatization

Observational research shows that individuals with anxiety are still stigmatized by their direct environment.[35,36] Stigmatizing attitudes like stereotyping people with anxiety as weak or incapable directly affect a person's life and are also associated with delayed treatment seeking and mental distress.[35] The importance of addressing feelings of anxiety together with other mental health concerns in elite athletes was highlighted in the consensus statement of the International Olympique Committee published in 2019.[37] Since then, several famous athletes publicly shared their personal struggles in public and research focusing more and more on burnout and psychological readiness to return to sport.[20,25,31,38–40] Already in the preprofessional phase mental health care should be available to athletes. In Chapters 3 and 4 the focus of the participants and their caregivers and staff of the dance academy seemed primarily on the physical performance of our sample, with less attention given to their psychosocial functioning. Consequently, the adolescents' environment could negatively impact their functioning and possibly lead to neglect of anxiety.

Adolescents are particularly vulnerable to anxiety due to numerous stressors during this life phase and barriers to seeking help.[41,42]. Adolescence is also the peak age for the risk of onset of mental health disorders.[43] The stigma on these complaints during adolescence was illustrated in a study on adolescents with symptomatic GJH comparing self-reported psychological distress to clinical evaluation. They found that these adolescents tended to focus on the physical aspects of their complaints while downplaying psychological distress, including anxiety.[44,45] While in adults with symptomatic GJH general anxiety, social anxiety and kinesiofobia are frequently reported. Addressing anxiety may be crucial in safeguarding long-term well-being to prevent it from becoming a chronic issue that negatively affects daily life and societal participation. Adolescents may need help by prioritizing their long-term health instead of focusing on short term goals.[46] While our sample in Chapters 3 and 4 showed a high prevalence of anxiety that persisted over time, it remains unclear whether these individuals' faced barriers or stigma when seeking help.[35,41] It could be that they

were self-conscious towards anxiety and experience like for example the fear of failure, but that they are unaware how anxiety can also impact physical and psychosocial functioning.

General conclusion

The main findings indicate that individuals with symptomatic GJH experience higher levels of general anxiety, social anxiety, and kinesiophobia (Chapter 5). These anxieties stem from challenges associated with GJH, such as joint instability and chronic pain, aligning with established patterns of pain-related fear and disability described in the Fear-Avoidance Model (FAM).[1,11] If pain-related disability is detected in adolescents with GJH using the DCALI, this should lead to an assessment of the impact of psychological factors such as fear and anxiety on their disability (Chapter 2).

In asymptomatic GJH, anxiety may pre-exist due to adolescence or a high-demand environment, worsening in the presence of pain (Chapter 3 and 4). Anxiety is multidimensional, encompassing fear of failure, performance anxiety, and anxiety related to GJH. While GJH-related anxiety is present, fear of failure and performance anxiety appear to have a greater influence on physical behaviour.

Rather than avoidance, high-performing dancers with GJH and elevated anxiety often adopt maladaptive coping strategies, leading to overuse, exhaustion, and, ultimately, disability or dropout (Chapter 3 and 4).

Anxiety had a clear disabling role in the high-performing adolescents with asymptomatic GJH and anxiety in Chapter 3 and 4, yet these adolescents did not meet the diagnostic criteria of anxiety as a core comorbidity according to the current diagnostic framework.[1]

Suggesting that the diagnostic framework of of Tofts et al.[1] should be more permissive allowing the presence of increased levels of anxiety as core comorbidity. This will enable trainers and caregivers around adolescents with asymptomatic GJH to be more aware of the disabling role of anxiety. While joint hypermobility is the primary clinical feature in asymptomatic GJH some individuals may develop clinical symptoms over time and anxiety, even pre-existent, may be the trigger in case of pain.

Anne started her preprofessional dance career at the ATD with the presence of GJH and anxiety. Het coping mechanism for her fear of not being able to stand out or even keep up with her peers made her take on an extra training load.

Based on the findings of this dissertation Anne was at risk for dropout based on her GJH and anxiety symptoms. Her coping mechanism showed similarities with the endurance-related pain response and entering in a negative spiral of overuse might result in disability and dropout.

The psychological care team within the dance academy educated Anne how to cope with GJH in elite sports and how anxiety could affect her physical and mental functioning. She received tools to coop with her fear of failure and the pressure of the expectations of her environment.

Methodological considerations

Taxonomy

In Chapter 3 and 4 we studied high-performing dancers between 16 and 24 years of age. In our studies we assessed the presence of GJH when a Beighton score 5 out of 9 is present. The consensus statement of 2017 provided clear definitions regarding clinical diagnosis of Ehlers-Danlos Syndrome (EDS).[2] The cut-off of the Beighton Score for the definition of GJH in adolescents is set on ≥6 out of 9 while in pubertal men and women up to the age of 50 a cutoff ≥5 out of 9 is used.[2] The age range of adolescents and pubertal men and women overlaps with adolescence being defined between 10 and 19 years of age and puberty starting at 10 years of age in girls and 13 years of age in boys.[47,48] Using the cut-off of ≥5 may have caused increased diagnosis of GJH compared to ≥6. The data of the studies reported in Chapter 3 and 4 were conducted before the consensus statement of 2017. In the review described in Chapter 5 studies were included that predated or did not adhere to the 2017 consensus statement. Therefore, we choose to use the terms “asymptomatic” and “symptomatic GJH”. In future studies in (a)symptomatic GJH we advise to use the consensus statement criteria of 2017.

Study population

The interest in psychosocial factors within GJH is growing. In children and adolescents’ new insights in the relationship between anxiety and GJH raising awareness for psycho-

social factors within GJH.[49–51] Most research has been conducted in symptomatic children and adolescents. We tried to include an asymptomatic group of adolescents with GJH in Chapter 3 and 4. However based on our findings we may conclude that having both GJH and anxiety could be considered as symptomatic GJH, potentially leading to decreased physical functioning and societal participation.

Outcome measures

To assess anxiety, we used generic tools. The underlying nature of these anxiety symptoms, such as fear of injury, movement, or other types of anxiety, was not explored. Future studies are recommended to investigate performance anxiety and fear of injury or movement, including their potential implications for interventions. Suitable measurement tools for assessing performance anxiety have been outlined by Patel et al.,[52] and for fear of injury and movement by Ambegaonkar et al.[53] Also, the threshold for the cutoff to detect anxiety with the Hospital Anxiety and Depression Scale differs between studies. Both scores equal or greater to 8, 10 and 11 points out of 21 are used to define increased anxiety.[32,54,55] In our samples we used the cutoff of equal or greater to 8 points. The participants in Chapters 3 and 4 were in a highly competitive environment and not likely to report any psychosocial complaints. To create a safe space for our sample, we did not share personal data with the Dance Academy. Still, information bias may have occurred.

In Chapter 3 and 4 we chose a sample of individuals that seemed to benefit from their GJH to assess the impact and association of GJH and anxiety. Although we recognized their vulnerability to injuries, we had not foreseen that this sample would have such decreased levels of physical functioning. Therefore, we used generic tools to assess physical functioning and anxiety and did not include our newly validated DCALI to assess disability in daily life.

Implications for clinical practice

Screening of GJH and anxiety in adolescents is only recommended in groups with an increased GJH prevalence and a high demanding environment like the performing arts as well as sports and not primarily in the general population. This could be part of the regular intake or audition at the dance education and should be incorporated within professional dance training programs and companies. We recommend educating all high-performing adolescents with GJH on how anxiety can impact functioning which may encourage them to seek help at an early stage. Institutes for professional dance training programs should not only invest in promoting mental literacy but also match the needs of the high-performing

adolescent dancers, staff and coaches.[53] They expressed an explicit interest in injury management and psychological subjects.[53] Including positive coping skills like visualization, relaxation techniques and goal setting may possibly replace the maladaptive coping styles like denial and suppressing pain or injuries that the high-performing adolescent dancers may have.[56]

Those with an increased anxiety should be monitored to care for both the physical- and psychosocial functioning of the individual dancer and prevent them from early dropout or retiring. When entering the healthcare system with a physical complaint or a psychosocial problem as the primary indication, clinicians or healthcare professionals should be aware of the possible co-occurrence of the presence of GJH and anxiety or fear symptoms and their associations.

Educating patients on the role of anxiety in GJH and physical and psychosocial functioning is then advised. When GJH results in disability and anxiety, or fear prolonged over time and is not treatable by a monodisciplinary allied healthcare professionals an interdisciplinary team should be consulted in which besides the health care professionals focusing the musculoskeletal system also other health care professionals (e.g. psychologist, occupational therapist and a physiatrist) should participate. In longitudinal follow up studies and tailored interventions we advise to focus on physical- and psychosocial domains (training and trainability, behavioral changes and nutrition).

Future research suggestions

Future research should focus on increasing our knowledge and understanding about the complexity of GJH and the impact of anxiety in adolescents with asymptomatic GJH. First, to track the progression of changes of GJH from adolescence into adulthood, longitudinal studies are necessary in assessing how anxiety and other psychosocial factors evolve and impact physical- and psychosocial functioning over time. When addressing anxiety, it is important to understand the possible barriers for these adolescents to report anxiety symptoms. Examining the type of anxiety and the role of environmental factors in the development and exacerbation of GJH-related symptoms could provide valuable insight into personalized treatment approaches and care. Therefore, studies must examine the implementation and impact of educational programs within high-demanding environments, such as performing arts and sports, to determine best practices for supporting high-performing adolescents with asymptomatic GJH. Additionally, the effectiveness of educational programs should be assessed in decreasing the disabling effects of anxiety and

improving overall outcomes for adolescents with (a)symptomatic GJH. Focusing on these domains can contribute to a better understanding and effective management strategies for adolescents with asymptomatic GJH and their associated challenges.

Implications for education

A biopsychosocial approach is essential in understanding the risk and impact of complaints related to GJH on functioning in daily life and societal participation. Therefore, future healthcare professionals (students) from various backgrounds should learn to apply this approach, using a holistic view of health to enhance their communication and collaboration skills. Existing frameworks like the International Classification of Functioning (ICF), that "conceptualises functioning as a 'dynamic interaction between a person's health condition, environmental factors and personal factors'".[57] The ICF exists of 5 domains, personal factors, environmental factors and health condition is divided in three different domains, body structures and functions, activities and participation. By utilizing validated and reliable assessment tools within the different domains of the (ICF), clinical reasoning can be effectively performed, allowing for objective conclusions about general health and psychosocial functioning. Also curricula of healthcare studies should focus on selective prevention to acknowledge the importance to prevent individuals with an increased risk for a specific illness or health problem and consequent disability. Proactive clinicians and health care professionals are needed in adolescent environments where patterns for healthy lifestyle should be embedded.

Allied health professionals, educators, coaches, and trainers working with adolescents with GJH, whether in a school setting or specifically in sports environments like dance, should be educated about the symptoms of GJH, its impact on functioning, and the role of anxiety in adolescents with asymptomatic GJH as well as tailored (interdisciplinary) interventions.

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Chapter 7

Summary
Samenvatting

Summary

In **Chapter 1**, we present a general introduction of the full spectrum of Generalized Joint Hypermobility (GJH), from isolated GJH to Hereditary Connectives Tissue Disorders (HCTDs) as the Ehlers-Danlos syndrome. We outline the current literature on the impact of GJH on functioning and the physical and psychological factors related to GJH. Furthermore, the ICF-CY model and the Beighton score are introduced.

GJH is a condition characterized by the ability to move joints beyond the "normal" range of motion. While some may have GJH without significant issues, others may develop musculoskeletal and systemic problems, leading to disability when injured. Perceived disability and clinical presentations may change over time and recognizing GJH and its associated symptoms is critical particularly in differentiating it from HCTDs.

The frequent experience of pain in hEDS can induce pain-related fear and anxiety and may lead to avoidance, discomfort and disuse. Alongside physical problems, anxiety and fear could play a significant role in worsening disability. Whether this is also the case for adolescents and young adults with asymptomatic GJH is currently unknown.

Chapter 2 presents the validation of the Dutch Child Activity and Limitations Interview (DCALI). After translation, we assessed construct validity through hypothesis testing and internal consistency via exploratory factor analysis, finding both to be strong. The DCALI is introduced for adolescents with chronic musculoskeletal pain to evaluate pain-related disability, distinguishing between routine and physically demanding activities. Our findings provide a useful clinimetric tool to help clinicians identify and address disability caused by pain.

Chapter 3 and 4 explore the impact of generalized joint hypermobility (GJH) and anxiety on functioning and dropout risk in high-performing adolescent dancers. We grouped participants based on hypermobility and anxiety, assessing their physical and psychosocial functioning. Adolescents with both GJH and anxiety demonstrated decreased functional outcomes compared to peers without GJH or anxiety. Those with GJH but no anxiety had functional outcomes similar to non-GJH peers. Over time, the combination of GJH and anxiety was linked to a higher dropout risk compared to peers without GJH and those with GJH but no anxiety. Furthermore, fatigue levels increased among all high-performing dancers, posing a serious risk for sick leave and work disability. In conclusion, the combination of GJH and anxiety has significant impact on the functioning and dropoutrisk of high-performing adolescent dancers and the increase of fatigue levels among all dancers show a serious

risk. These findings demand a systemic screening for GJH and anxiety of these athletes to enable better support from clinicians and staff to help reduce the associated risk of injury, drop-out and disability.

Chapter 5 reviews the current literature concerning GJH with and without complaints and anxiety in all life phases. We included 32 studies of which eight included a population of adolescents and young adults and 22 studies included adults above 21 and two studies included populations with overlapping agegroups. In total 11 studies included populations with GJH but without complaints. Two third of the selected studies were performed in the last decade indicating a rising interest in the interaction between anxiety and GJH. Individuals with GJH and complaints reporting increased levels of anxiety than those those without complaints and the general population indicating that higher levels of anxiety are related to the different stages in the spectrum of hypermobility. While anxiety in adolescents and adults with GJH without complaints falls within normal to moderate ranges, it remains significantly elevated compared to the general population. Notably, contradictory results were found regarding specific anxieties and fears in GJH without complaints, while increased scores were noted in those with complaints. Anxiety in adults with Hypermobility Spectrum Disorder (HSD) and hypermobile Ehlers-Danlos Syndrome (hEDS) aligns with anxiety seen in other chronic pain populations. Our findings emphasizes the importance of screening for anxiety in all types of GJH and acknowledges the barriers adolescents and young adults may face in expressing anxiety symptoms. We recommend screening of anxiety screening in highperforming individuals with GJH, regardless of whether they have complaints, and support an interdisciplinary approach for those who do.

Samenvatting

Hoofdstuk 1 geeft een algemene introductie van het volledige spectrum van Gegeneraliseerde Gewrichtshypermobiliteit (GJH), van GJH zonder klachten tot Erfelijke Bindweefselaandoeningen zoals het Ehlers-Danlos syndroom (EDS). We beschrijven de huidige literatuur over de impact van GJH op het functioneren en de fysieke en psychologische factoren die verband houden met GJH. Verder worden het ICF-CY model en de Beighton score geïntroduceerd.

GJH is een aandoening die wordt gekenmerkt door het vermogen om gewrichten verder te bewegen dan de "normale" bewegingsvrijheid. Terwijl sommigen GJH hebben zonder significante problemen, kunnen anderen musculoskeletale en systemische problemen ontwikkelen, wat kan leiden tot invaliditeit bij letsel. Waargenomen invaliditeit en klinische presentaties kunnen in de loop van de tijd veranderen en het herkennen van GJH en de bijbehorende symptomen is cruciaal, vooral bij het onderscheiden van erfelijke bindweefselaandoeningen. Doordat bij hypermobiele Ehlers-Danlos (hEDS) frequent pijn wordt ervaren, kan dit pijn-gerelateerde angst en vrees veroorzaken, wat kan leiden tot vermijding, ongemak en inactiviteit. Naast fysieke problemen kunnen angst en vrees een belangrijke rol spelen bij het verergeren van invaliditeit. Of dit ook het geval is bij adolescenten en jongvolwassenen met asymptomatische GJH is momenteel onbekend.

Hoofdstuk 2 presenteert de validatie van het Nederlandse Child Activity and Limitations Interview (DCALI). Na vertaling hebben we de constructvaliditeit beoordeeld door middel van hypothesetesten en de interne consistentie via exploratieve factoranalyse, waarbij beide sterk bleken te zijn. De DCALI wordt ingezet bij adolescenten met chronische musculoskeletale pijn om pijn-gerelateerde invaliditeit te evalueren, waarbij onderscheid wordt gemaakt tussen routinematige en fysiek veeleisende activiteiten. Onze bevindingen bieden een nuttig meetinstrument om clinici te helpen bij het identificeren en aanpakken van beperkingen veroorzaakt door pijn.

Hoofdstukken 3 en 4 onderzoeken de impact van gegeneraliseerde gewrichtshypermobiliteit (GJH) en angst op het functioneren en het risico op uitval bij hoogpresterende adolescente dansers. We hebben deelnemers gegroepeerd op basis van hypermobiliteit en angst, waarbij we hun fysieke en psychosociale functioneren beoordeelden. Adolescenten met zowel GJH als angst vertoonden verminderde functionele uitkomsten vergeleken met leeftijdsgenoten zonder GJH of angst. Degenen met GJH maar zonder angst hadden functionele uitkomsten vergelijkbaar met leeftijdsgenoten zonder GJH. In de tijd werd de

combinatie van GJH en angst gekoppeld aan een hoger risico op uitval vergeleken met leeftijdsgenoten zonder GJH en degenen met GJH maar zonder angst. Bovendien nam de vermoeidheid toe bij alle hoogpresterende dansers, tot een niveau dat het een ernstig risico vormt voor ziekteverzuim en arbeidsongeschiktheid. Concluderend heeft de combinatie van GJH en angst een significante impact op het functioneren en het uitvalrisico van hoogpresterende adolescente dansers en de toename van vermoeidheid bij alle dansers toont een ernstig risico. Deze bevindingen vragen om een systematische screening op GJH en angst bij deze atleten om betere ondersteuning van clinici en staf mogelijk te maken en het bijbehorende risico op letsel, uitval en invaliditeit te verminderen.

Hoofdstuk 5 bespreekt de huidige literatuur over GJH met en zonder klachten en angst in alle levensfasen. We hebben 32 studies opgenomen, waarvan acht een populatie van adolescenten en jongvolwassenen omvatten; 22 studies omvatten volwassenen boven de 21 en twee studies omvatten populaties met overlappende leeftijdsgroepen. In totaal omvatten 11 studies populaties met GJH maar zonder klachten. Twee derde van de geselecteerde studies werd uitgevoerd in het afgelopen decennium, wat wijst op een groeiende interesse in de interactie tussen angst en GJH. Personen met GJH en klachten rapporteren hogere niveaus van angst dan degenen zonder klachten en de algemene bevolking, wat aangeeft dat hogere niveaus van angst verband houden met de verschillende stadia in het spectrum van hypermobiliteit. Hoewel angst bij adolescenten en volwassenen met GJH zonder klachten binnen normale tot matige grenzen valt, zijn deze scores significant hoger in vergelijking met de algemene bevolking. Opmerkelijk zijn de tegenstrijdige resultaten met betrekking tot specifieke angsten bij GJH zonder klachten, terwijl verhoogde scores werden opgemerkt bij degenen met klachten. Angst bij volwassenen met Hypermobiliteit Spectrum Stoornis (HSD) en hEDS komt overeen met angst die wordt gezien bij andere chronische pijnpopulaties. Onze bevindingen benadrukken het belang van screenen op angst bij alle soorten GJH en erkennen de barrières die adolescenten en jongvolwassenen kunnen ondervinden bij het uiten van angstklachten. We pleiten voor het screenen van angst bij individuen met GJH in een topsportomgeving, ongeacht of ze klachten hebben, en ondersteunen een interdisciplinaire aanpak voor degenen die klachten hebben.

Appendices

Authors' contributions
About the author
PhD portfolio

Authors' contributions

Chapter 2

The Dutch version of the self-report Child Activity and Limitations Interview in adolescents with chronic pain.
Janneke E. de Vries, Carolien Dekker, Carolien H.G. Bastiaenen, Mariëlle E.J. B. Goossens, Raoul H.H. Engelbert, Jeanine A. M. C. F. Verbunt
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JdV participated in the design of the study, analysed and interpreted the data and wrote the manuscript. CD participated in the design of the study, assisted in the data analysis and reviewed the manuscript. CB assisted in the design of the study and reviewed the manuscript. MG assisted in the design of the study, and reviewed the manuscript. RE assisted in the design of the study and reviewed the manuscript. JV conceived the study, participated in its design and coordination of datacollection and reviewed the manuscript.

Chapter 3

Generalized Joint Hypermobility and Anxiety in Adolescents and young Adults, the Impact on Physical and Psychosocial Functioning.
Janneke E. de Vries, Jeanine A. M. C. F. Verbunt, Bart Visser, Stephan P. J. Ramaekers, Patrick Calders, and Raoul H.H. Engelbert
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Conceptualization, J.d.V., J.V., and R.E.; methodology, J.d.V., J.V., B.V., and R.E.; validation, J.d.V., R.E., and B.V.; formal analysis, J.d.V.; investigation, J.d.V., R.E., and B.V.; data curation, S.R., J.d.V., and P.C.; writing—original draft preparation, J.d.V. and J.V.; writing—review and editing, J.V., R.E., and J.S.; supervision, R.E., P.C., and J.V.; project administration, R.E. and S.R. All authors have read and agreed to the published version of the manuscript.

Chapter 4

Generalized Joint Hypermobility and Anxiety Are Serious Risk Factors for Dysfunctioning in Dance Students: A One-Year Follow-Up Study.
Janneke E. van Die-de Vries, Jeanine A. M. C. F. Verbunt, Stephan P. J. Ramaekers, Patrick Calders, Raoul H. H. Engelbert
International Journal of Environmental Research and Public Health 2022,19,2662
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Conceptualization, J.v.D.-d.V., J.V., and R.E.; methodology, J.v.D.-d.V., P.C., and R.E.; validation, J.v.D.-d.V. and R.E.; formal analysis, J.v.D.-d.V.; investigation, J.v.D.-d.V., R.E., and S.R.; data curation, S.R., J.v.D.-d.V., and P.C.; writing—original draft preparation, J.v.D.-d.V., P.C., and S.R.; writing—review and editing, J.V., R.E. and S.R..; supervision, S.R, R.E., P.C., and J.V.; project administration, R.E. and S.R. All authors have read and agreed to the published version of the manuscript.

Chapter 5

The role of anxiety in individuals with Generalized Joint Hypermobility. A systematic review.
Janneke E. van Die-de Vries, Eugene A. A. Rameckers, Patrick Calders, Raoul H. H. Engelbert, Stephan P. J. Ramaekers, Mariëlle E.J. B. Goossens, Jeanine A. M. C. F. Verbunt
Arch Rehabil Res Clin Transl. 2025 May doi: 10.1016/j.arrct.2025.100467

JvD participated in the design, performed the search, selection, analysed and interpreted the data and wrote the manuscript. ER participated in the design, performed the selection, analysed the data and reviewed the manuscript. PC assisted in the design of the study and reviewed the manuscript. RE assisted in the design of the study and reviewed the manuscript. SR participated in the design of the study, analysed the data and reviewed the manuscript. MG participated in the design of the study, assisted in interpretation of the data and reviewed the manuscript. JV conceptualized the study, participated in the design and supervised the analysis and interpretation of the data and reviewed the manuscript.

About the author

Early life and education

Janneke was born on November 24, 1987, in Hoofddorp, the Netherlands, where she also grew up. She pursued her undergraduate studies in Physical Therapy at the Amsterdam University of Applied Sciences (HvA). Her Bachelor Thesis was awarded the Jaco den Dekker Thesis Award by the Royal Dutch Society for Physiotherapy. Janneke graduated as a Physical Therapist in 2010. In 2012, she completed her Master's degree in Evidence-Based Practice in Health Care at the University of Amsterdam.

Professional career

Following her graduation, Janneke began her career as a physical therapist at Fysiotherapiepraktijk Diemen. At the same time, she took on a role as a teacher and researcher at the HvA, participating in research on hypermobility.

In 2014, Janneke received a Doctoral Grant for Teachers from the Dutch Research Council (NWO), enabling her to further explore psychosocial factors related to generalized joint hypermobility (GJH) during her PhD studies.

Research and collaboration

Janneke developed a screening protocol to evaluate the general health in physical, psychosocial factors and nutrition of patients with GJH. A pilot for the screening tool was performed in hypermobile dancers. An altered version was developed as part of a project in an international collaboration among GJH research groups in Belgium and the Netherlands of patients with HSD and hEDS. Janneke was responsible for the execution of this protocol to evaluate a patient group with HSD and EDS of our partners at the medical genetics department in Ghent University Hospital. We helped to objectify disease progression and outcomes were used in altering rehabilitation trajectories for individual patients. Janneke was committed to integrating her research with her students' learning experiences. She actively involved students from different faculties in data collection, allowing them to participate in measurements of the screening protocol specialized for GJH populations. Over a hundred students participated in the measurements either with the dancers or the partners patient groups with HSD or EDS. In 2012 this connection between research and education was rewarded when Janneke won the HvA Research

Battle with a presentation of a pilot study of the screening in hypermobile dancers. In 2015, Janneke established a partnership with the Amsterdam School of Theater and Dance, where she developed and implemented a screening protocol to assess students, which is now incorporated into the master's program in Performance, Sport, and Health. At the same time Janneke became part of the research group of the rehabilitation department of the Maastricht University that has expertise on chronic pain. Here she validated measurement tools to define fear of pain and pain-related disability in adolescents with chronic pain. Adolescents with chronic pain are treated with a multidisciplinary approach in the Maastricht University medical Center and the Adelante Rehabilitation Centre. Measurement tools that were validated help caregivers assess the impact of pain and anxiety or fear on daily functioning of the adolescent.

Additionally, from 2019 to 2021, she served as the head of research for SCORES (Developing Skills & Competences Resulting in Employability through Sport), an initiative focused on the dual careers of athletes. This project addressed employability and support services for young athletes seeking careers outside of sports, collaborating with stakeholders from five European countries: Spain, Finland, Italy, Bulgaria, and the Netherlands.

Throughout her PhD, Janneke remained a teacher at the HvA, actively involved in writing and teaching Evidence-Based Practice courses. In 2022, she took on the responsibility of coordinating the third and final year of the Bachelor's program in Physical Therapy. In 2024, she participated in developing specialized programs for the new Bachelor's curriculum in Physical Therapy education at the HvA.

Recently, Janneke created content for the HUB "voor het kind in beweging", an online development platform for physical therapists specializing in pediatrics. Her research aims to further understand the role of anxiety in GJH and understand why GJH does not influence daily life of one while it disables the life of others at the same time.

In her spare time, Janneke loves to play tennis and cook. She is married to Alain, and are proud parents of Benthe (2021) and Barend (2023).

PhD portfolio

Name PhD student: Janneke Eline de Vries
PhD period: 2014-2024
Name PhD supervisor: Prof. Dr. R.H.H. Engelbert and Prof. Dr. J.A.M.C.F. Verbunt
Name co-supervisors: Dr. S.P.J. Ramaekers and Prof. Dr. P. Calders

1. PhD training	Year	ECTS
General courses		
- Scientific writing in English for publication. Graduate School for medical sciences, University of Amsterdam, Amsterdam, the Netherlands	2016	1.5
- Presenting in English. Graduate School for medical sciences, Graduate School for medical sciences, University of Amsterdam, Amsterdam, the Netherlands	2017	1.0
- Basic course legislation and organization (eBROK). Graduate school for medical sciences, University of Amsterdam, Amsterdam, the Netherlands	2018	1.5
Specific courses		
- Cardiopulmonary Exercise Testing and Interpretation (CPET), Amsterdam University of Applied Sciences, Amsterdam, the Netherlands	2015	1.0
- Explain Pain Supercharged, Lorimer Mosely, Amsterdam, the Netherlands	2020	2.0
Presentations		
- Hypermobility in Young Dancers. *Oral presentation*, Research Battle, Amsterdam University of Applied Sciences, Amsterdam, the Netherlands	2012	0.5
- Hypermobility in Young Dancers. *Oral presentation*, Research Battle, Amsterdam University of Applied Sciences, Amsterdam, the Netherlands	2014	0.5
- Hypermobility in adolescent dance students. *Oral presentation*, Research meeting, Amsterdam University of Applied Sciences, Amsterdam, the Netherlands	2014	0.5
- Measurement instruments for adolescents with chronic pain. *Poster presentation*, PhD symposium: “Bijzonder bijzonder”. Adelante, Hoensbroek, the Netherlands	2015	0.5
- Joint laxity in dancing adolescents. *Oral presentation*, Musicians, Health, and Performance, Second conference, Odense, Denmark	2015	0.5
- Screening outcomes of 2015. *Oral presentation*, Research meeting, Amsterdam University of the Arts, Amsterdam, the Netherlands	2015	0.5
- Screening outcomes of 2016. *Oral presentation*, Research meeting, Amsterdam University of the Arts, Amsterdam, the Netherlands	2016	0.5
- Psychosocial factors and physical fitness in young professional dance students a follow up. *Oral presentation*, Research meeting, Amsterdam University of Applied Sciences, the Netherlands	2016	0.5
- Physical Fitness and Psychosocial Behavior in young professional dancers: Dance Screening. *Oral presentation*, International Association for Dance Medicine & Science, Texas Houston, United States	2017	0.5
- Physical and psychosocial functioning in young professional dance students with generalized joint hypermobility. *Oral presentation and workshop*, International Association for Dance Medicine & Science, Texas Houston, United States	2017	0.5
- Screening outcomes of 2017. *Oral presentation*, Research meeting, Amsterdam University of the Arts, Amsterdam, the Netherlands	2017	0.5

	Year	ECTS
- Physical fitness generalized joint hypermobility and psychosocial behavior in young professional dancers. *Poster presentation*, International Association for the study of Pain, Boston, United States	2018	0.5
- Psychosocial- and physical functioning in hypermobile Ehlers-Danlos Syndrome: a 5-year follow-up study. *Poster presentation*, International Symposium on Ehlers-Danlos Syndromes, Ghent, Belgium	2018	0.5
- Longitudinal Screening outcomes and clinical implications. *Oral presentation*, Research meeting, Amsterdam University of the Arts, Amsterdam, the Netherlands	2019	0.5
(Inter)national conferences		
- International EDS Symposium, Ghent, Belgium	2012	1.0
- Annual Congress of the European Alliance of Associations for Rheumatology, EULAR. Paris, France	2014	1.0
- Musicians Health and Performance, Second conference, Odense, Denmark	2015	1.0
- Know more – Do Better, Codarts Rotterdam, Rotterdam, the Netherlands	2015	1.0
- Ehlers-Danlos Syndrome International Symposium, New York, United States	2016	1.0
- International Association for the study of Pain World Congress on Pain 2018, Boston, United States	2018	1.0
- International Symposium on Ehlers-Danlos Syndromes, Ghent, Belgium	2018	1.0
- Symposium Exposure bij chronische pijn: Do or dare?	2018	1.0
Other		
- Measuring Physical Fitness and Psychosocial status in young professional dancers. *Workshop*, Amsterdam University of the Arts, Amsterdam, the Netherlands	2016	0.5

2. Teaching		
	Year	ECTS
Lecturing		
- Training Standardized Operating Procedures students at the Amsterdam University of Applied Sciences, Amsterdam	2012, 2015–2017	4.0
- Clinical Reasoning, Evidence Based Practice, Scientific Writing. Amsterdam University of Applied Sciences, European School of Physiotherapy, Amsterdam	2014–Present	4.0
- Evidence Based Practice. Minor Rehabilitation and Minor Children paramedical. Amsterdam University of Applied Sciences, Amsterdam	2017–Present	4.0
Tutoring, mentoring		
- Master student thesis: Is there an association between experienced pain and endurance in professional dancers (Scherer & Frijters 2015)	2015	1.0
- Master student thesis: Pain catastrophizing and Vigilance in Professional dance students (Helmes 2017)	2017	1.0
Other		
- Developing Evidence Based Practice modules within the educational curriculum	2022	4.0

3. Parameters of esteem	
	Year
Grants	
- Doctoral grant for teachers from the Dutch Research Council (NWO)	2014
Awards and prizes	
- Jury winner Research Battle, Amsterdam University of Applied Sciences	2012
- Jaco den Dekker thesis prize, the Royal Dutch Society for Physiotherapy	2009

4. Publications	
	Year
Peer reviewed	
- van Die-de Vries J, Verbunt J, Ramaekers S, Calders P, Engelbert R. Generalized Joint Hypermobility and Anxiety Are Serious Risk Factors for Dysfunctioning in Dance Students: A One-Year Follow-Up Study. Int J Environ Res Public Health. 2022 Feb 25;19(5):2662. doi: 10.3390/ijerph19052662. PMID: 35270355; PMCID: PMC8910411.	2022
- de Vries J, Verbunt J, Stubbe J, Visser B, Ramaekers S, Calders P, Engelbert R. Generalized Joint Hypermobility and Anxiety in Adolescents and Young Adults, the Impact on Physical and Psychosocial Functioning. Healthcare (Basel). 2021 Apr 29;9(5):525. doi: 10.3390/healthcare9050525. PMID: 33946940; PMCID: PMC8146775.	2021
- de Vries JE, Dekker C, Bastiaenen CHG, Goossens MEJB, Engelbert RHH, Verbunt JAMCF. The Dutch version of the self-report Child Activity and Limitations Interview in adolescents with chronic pain. Disabil Rehabil. 2019 Apr;41(7):833-839. doi: 10.1080/09638288.2017.1407969. Epub 2017 Nov 29. PMID: 29185366.	2017
- Dekker C, Bastiaenen CHG, de Vries JE, Simons LE, Goossens MEJB, Verbunt JAMCF. Dutch version of the Fear of Pain Questionnaire for adolescents with chronic pain. Disabil Rehabil. 2018 Jun;40(11):1326-1332. doi: 10.1080/09638288.2017.1289255. Epub 2017 Mar 3. PMID: 28637153.	2017