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ANXIETY & JOINT HYPERMOBILITY: CONNECTING MIND AND BODY

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DOCTORAL THESIS

ANXIETY & JOINT HYPERMOBILITY: CONNECTING MIND AND BODY

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**Cover image: "Drawing hands" by M.C. Escher.*

Professor Thomas Wise (director) and Professor Antonio Bulbena Vilarrasa (tutor) certify that they have supervised and guided this doctoral thesis presented by Andrea Bulbena-Cabre **"Anxiety & Joint hypermobility: connecting mind and body".** They hereby assert that this doctoral thesis fulfils the requirements to be defended.

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Javi, por muchas más victorias juntos.

A la meva meravellosa familia,

per ser però sobretot per estar.

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1 ABSTRACT

1.1 ENGLISH VERSION

Anxiety disorders are currently considered the most prevalent psychiatric illness across all ages and cause significant disability, which represent a burden to society. The nosology of anxiety disorders has changed significantly during the past centuries. While old concepts like neurosis embraced organic models of anxiety, in which symptoms of anxiety were interpreted in the context of medical illnesses, new nosological classification has moved towards the psychological, cognitive and behavioral aspects of anxiety. However, some studies reported the greatest proportion of the cost of anxiety is attributed to lost or reduced productivity, and the direct costs of medical treatment due to the unexplained physical or somatic symptoms. New models of somatic comorbidity among anxiety disorders have emerged over the past years and in this project, we focus on the relationship between the Joint Hypermobility Syndrome (also known as Ehlers Danlos-Hypermobile type (JHS/hEDS)) and Anxiety disorders, which was described for the first time over 30 years ago. We aimed to further study this association along with the underlying mechanisms with the ultimate goal of understanding the different dimensions of the psychopathology associated with JHS/hEDS.

A literature reviews confirm an increasing amount of evidence pointing towards a high prevalence of psychiatric conditions among individuals with JHS/hEDS. Particularly, JHS/hEDS is strongly associated with anxiety and there is also limited but growing evidence that JHS/hEDS is also associated with depression, eating and neuro-developmental disorders as well as alcohol and tobacco misuse. In the area of anxiety disorders, clinical and nonclinical studies confirm the solid association between JHS and anxiety. Specifically, JHS has been found to be associated with higher frequency of the so-called endogenous anxiety disorders (panic disorders and agoraphobia) along with higher intensity of anxiety and fears and greater physical and somatic complaints. In one of the studies included in this thesis, we have proven that this association is also maintained in elderly populations.

The underlying mechanisms behind this association include genetic risks, increased exteroceptive and interoceptive mechanisms and decreased proprioception. Recent neuroimaging studies have also shown an increase response in emotion processing brain areas which could explain the high affective reactivity seen in JHS/hEDS. In this thesis, we have also studied the autonomic nervous functioning in these patients and found that they have an atypical regulation of the ANS and are more likely to suffer from autonomic-related illnesses. These findings are in line with other studies that have shown that patients with JHS/hEDS are more likely to suffer from stress-related illnesses such as fibromyalgia or irritable bowel syndrome.

As part of this thesis, we developed a new model of somatic illness called the “Neuroconnective phenotype” in which the core includes the relationship between anxiety and joint hypermobility and the different somatic, psychological, cognitive and behavioral aspects are described. This phenotype should be implemented to ensure proper assessment and to guide for more specific treatments. Future lines of research should further explore the biological basis of this association and expand and develop the therapeutic dimension.

1.2 SPANISH VERSION

La ansiedad se considera actualmente la enfermedad psiquiátrica más prevalente en todos los rangos de edad, y además causa una invalidez considerable, lo que representa una carga para la sociedad. La nosología de los trastornos de ansiedad ha cambiado significativamente durante los últimos siglos. Aunque conceptos antiguos como la "neurosis" abarcaban modelos mixtos en los que los síntomas de ansiedad se interpretaban en el contexto de enfermedades médicas, la nueva clasificación nosológica ha ido migrando hacia los aspectos psicológicos, cognitivos y conductuales de la ansiedad. Sin embargo, la mayor proporción del coste de la ansiedad se atribuye a la pérdida o reducción de la productividad y a los costes directos del tratamiento médico debido a los síntomas físico o somáticos inexplicables. En los últimos años han surgido nuevos hallazgos y nuevos modelos de comorbilidad somática en los trastornos de ansiedad y en esta tesis nos centramos en la relación entre el síndrome de hiperlaxitud articular (también conocido como Ehlers-Danlos tipo Hypermobil (JHS/hEDS)) y los trastornos de ansiedad, que fue descrito por primera vez hace más de 30 años. Nuestro objetivo principal es revisar esta asociación junto con los mecanismos subyacentes con el fin de comprender las diferentes dimensiones de la psicopatología asociada con el JHS/hEDS.

La revisión de la literatura confirma una alta prevalencia de trastornos psiquiátricos en los individuos con el JHS/hEDS. Particularmente, el JHS/hEDS está fuertemente asociado con la ansiedad y también hay evidencia creciente de que también esté asociado con trastornos depresivos, alimentarios y del desarrollo, así como con el abuso de alcohol y tabaco. En el área de los trastornos de ansiedad, hay estudios clínicos y no clínicos que confirman la sólida asociación entre el JHS / hEDS y la ansiedad. Específicamente, se ha encontrado que el JHS / hEDS está asociada con una mayor frecuencia de los llamados trastornos de ansiedad endógenos (trastornos de pánico y agorafobia) junto con una mayor intensidad de ansiedad y temores y mayores quejas físicas y somáticas. En uno de los estudios presentados en este proyecto se confirma esta asociación en una población mayor de 60 años.

Los mecanismos subyacentes detrás de esta asociación incluyen riesgos genéticos, aumento de los mecanismos exteroceptivos e interoceptivos y disminución de la propiocepción. Recientes estudios de neuroimagen también han demostrado una mayor de respuesta en las áreas cerebrales que procesan emociones, lo podrían explicar la alta reactividad afectiva visto en estos sujetos. Asimismo, en esta tesis hemos estudiado el funcionamiento del sistema nervioso autónomo (ANS) en estos pacientes y hemos encontrado que tienen una regulación atípica del ANS y son más propensos a sufrir enfermedades relacionadas con este sistema. Estos hallazgos son congruentes con otros estudios que han demostrado que los pacientes con JHS / hEDS suelen sufrir enfermedades relacionadas con el estrés como la fibromialgia o el síndrome del intestino irritable.

Como parte de esta tesis, se ha desarrollado un nuevo modelo de enfermedad somática denominado "Fenotipo Neuroconnectivo" en el que se incluyen la relación entre la ansiedad y la hyperlaxitud articular en el núcleo y se describen los respectivos aspectos somáticos, psicológicos, cognitivos y de comportamiento. Este fenotipo debe ser implementado para asegurar una evaluación adecuada y para guiar para tratamientos más específicos. Futuras líneas de investigación deben explorar aún más las bases biológicas de esta asociación y ampliar y desarrollar la dimensión terapéutica.

2 INTRODUCTION

2.1 ANXIETY

Epidemiology

Anxiety disorders (AD) are the most prevalent mental illness in the general population [1]. They are chronic, very disabling and are estimated to be the sixth leading cause of disability worldwide [2]. Epidemiological studies indicate that when taken together anxiety disorders have a 12-month period prevalence of approximately 14%, and a lifetime prevalence of approximately 21% [3]. In general, they are more common in women in a ratio 2:1 compared to men and tend to decrease with age [4]. Despite the different anxiety disorders have specific symptoms, all of them have common emotional (uneasiness, fear), cognitive (negative thoughts, worry), behavioral (avoidance, attachment issues) and physical symptoms (tachycardia, muscle tension, dizziness).

Anxiety disorders are often underdiagnosed and untreated. They cause a significant burden to society and data collected in 1990 indicated that the total costs of anxiety disorders in the United States, reached approximately $46 billion, which is one third of the total cost for all mental disorders [5]. The costs associated with anxiety disorders were higher than those for schizophrenia ($32 billion), affective disorders ($30 billion), and other combined mental disorders ($38 billion). The greatest proportion of the cost of anxiety (nearly three quarters) is attributed to lost or reduced productivity, and the direct costs of medical treatment due to the unexplained physical or somatic symptoms.

Anxiety in the elderly population

Research focused on examining trends of psychiatric disorders among older age groups is limited [6] but is estimated that by 2050 there will be two billion of older adults globally with a corresponding increase in the number of older adults suffering anxiety disorders (AD) [7]. AD have historically been considered a problem of childhood and early adulthood, with a peak onset between 18 and 40 years. However, later studies demonstrate that the prevalence of

anxiety AD in community-dwelling older adults is 11%, suggesting a higher prevalence than late-life depression that is 6% approximately [6, 8]. The prevalence of late-life AD is even higher among homebound elderly nursing homes residents [9], older medical patients [10] and patients who have chronic medical illness [11, 12]. It is estimated that specific phobia is the most prevalent AD in older life followed by social phobia, generalized anxiety disorder, panic disorder and agoraphobia [8].

Several studies suggest that anxiety has a different presentation among older people as is often accompanied by co-morbid depression symptoms, and geriatric psychiatry research is struggling to understand the treatment needs of this co morbidity [8, 13]. For these reasons, AD in late life may be even more likely to be underdiagnosed than in younger groups, but they have a significant impact in terms of health care costs as people with anxiety disorders make heavy use of medical services [14]. AD as a primary cause for hospitalization increase exponentially with age, as do health care costs related to anxiety disorders; the annual U.S. health care costs due to late-life anxiety disorders in 1990 was estimated to be $42.3 billion [15]. AD are also associated with increased depression, decreased quality of life, reduced perceptions of physical and mental health and vitality, greater physical disability, poor quality of life, increased comorbidity, and increased use of health services [13, 14, 16].

Considering that early diagnosis and treatment of anxiety might be relevant to increase health gains in late-life, it would be of great interest to identify specific markers of anxiety in that age range for early identification of these disorders.

Rediscovering the concept of "neurosis"

Clinical and neurobiological data suggest that psychiatric disorders, as traditionally defined by the Diagnostic Statistical Manual of Mental Disorders 5 (DSM-5) are more comorbid than expected by chance, often share neurobiological features and alterations across multiple brain systems [17]. Current classification of anxiety disorders is characterized by many subjective

cognitive (anticipatory anxiety), behavioral (avoidance behavior) and psychological (worry, fear) aspects of anxiety, but the often-comorbid somatic or physical conditions are neglected.

Interestingly, the concept of anxiety has evolved significantly throughout history. According to Berrios [18] , descriptions of anxiety and fear reactions are found in the Greek mythology, when those who feared encountering the god Pan had panic attach like reactions [19]. In fact, it was not until the middle of the XIX century when it appeared as a psychopathological concept. At that time, anxiety symptoms were interpreted in the context of medical illnesses and Scottish psychiatrist William Battie (1703-1776) provided one of the earliest descriptions of anxiety in the medical literature, differentiating madness from the less serious anxiety that results from excessive stimulation of the nerves. Following this line, Dr. William Cullen (1710-1790) developed the concept of “neuroses” to describe a general disturbance of the nervous system without any observable lesion or dysfunction of the bodily organs. Later on, the concept of “neurosis”, in its golden age (the end of the XIX century), incorporated physical and mental manifestations that coexist harmoniously with descriptions such as "irritative weakness" and "intimate nervous system malnutrition" described by Erb, Bouchut, cerebrogastric neuropathy, neuropathy Krishaber's cerebrocardiaca, Mouneret's hyperreflexia, Cerise's protean neurosis, and many others. At the beginning of the XX century, Freud and his disciples injected an intense psychodynamic orientation into the concept that at the same time facilitated the expansion of the somatic dimension.

Unfortunately, the "neurosis" concept officially disappeared in 1980 with the DSM-III, although some rescue attempts were done by Peter Tyrer [20], who proposed the "general neurotic syndrome". This syndrome consisted of a wide symptomatology of anxiety and also depressive symptoms, which indeed are often comorbid.

However, despite the organic model of anxiety (in which symptoms of anxiety were interpreted in the context of medical illnesses), has persisted over many years, it has been substituted with the evolution of contemporary diagnostic symptoms. These new nosological classifications in

which the somatic and bodily manifestations are neglected, have made anxiety disorders difficult to identify and also to treat.

2.2 THE JOINT HYPERMOBILITY SYNDROME

Background

The term Joint Hypermobility Syndrome (JHS) was used for the first time in 1967 to describe the association of the joint laxity with some musculoskeletal diseases [21]. For many years, rheumatologists have studied this disorder, with an over-representation of the articular features and the name has varied as a result. Prof. Jaume Rotés used the term "Laxité articular" (articular laxity) in 1957 when he published a proposal with different sets of criteria to correctly diagnose this illness [22]. Interestingly, in this article, he also described a remarkable degree of nervous tension suffered by patients with greater joint laxity. Later on, in 1964, Carter and Wilkinson used also the term "articular laxity" in an article where they described some new diagnostic criteria [23]. Some years later, in 1973, Beighton published an epidemiological paper in which he used indistinctly "joint hypermobility" and "joint laxity" [24] and since then both terms are found in different papers. However, despite the name of the illness refers to the joints, its medical origin was most likely dermatological. A dermatologist from Denmark called Edward Ehlers described a patient with hyper-extensible skin along with greater mobility laxity and multiple bruises back in 1901. At the same, Henri-Alexandre Danlos, a French dermatologist, described the pseudo-tumors moluscoids in 1908. Both cases were presented concurrently at the "Société Parisienne de Vénérologie et Dermatologie" in Paris and were included as disorders of the connective tissue giving the name to the disorders of the Ehlers-Danlos Syndrome. Historically, there are 6 subtypes of Ehlers-Danlos syndromes and the most benign and common one is the Hypermobile type (hEDS). Literature uses indistinctly Joint Laxity, the Joint Hypermobility syndrome and Ehlers Danlos Syndrome-Hypermobile type (hEDS), and in this thesis, will use the acronym JHS/hEDS to refer to this illness.

This syndrome is a highly heritable collagen condition and is characterized by an increased distensibility of the joints in passive movements as well as a hypermobility in active movements in the absence of any rheumatologic disease [25]. The JHS/hEDS has a strong autonomic pattern; it is more frequent in women (3:1) and has an estimated prevalence of 10-15% in the general population [26], being more prevalent in Asians and Africans compared to Europeans [25]. However, the JHS goes usually underdiagnosed and its prevalence in the general population still remains unknown. By age groups, it is more common in youngsters and the frequency tends to decrease with age [27]. As noted in prior studies, the prevalence of JHS decreases in men in the third decade and in women in the fifth decade of life [27].

Associated features

The JHS/hEDS has a wide range of musculoskeletal and extra-articular symptoms which are associated with the collagen abnormality [28]. The most common articular symptoms include joint laxity, widespread joint pain, luxation/subluxations, and soft tissue and spine pain and soft tissue lesions. Over the recent years, the extra-articular features such as easy bruising, skin flexibility and organ prolapses among others have gained recognition.

Moreover, subjects with JHS frequently present with stress-sensitive illnesses such as fibromyalgia, irritable bowel disease, temporomandibular joint disorder and chronic fatigue syndrome [29]. See all the associated features in figure 1.

Figure 1. Musculoskeletal and extra-articular features of JHS/hEDS

Diagnosis

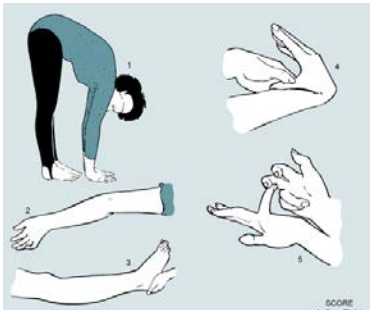
There are different sets of criteria that have been described to diagnose the JHS. The most common ones are the Beighton criteria that were described in 1969 [30]. They test the dorsiflexion of the fifth finger, the apposition of thumb, the hyperextension of elbows and knees and the trunk flexion. The maximum score is nine and the cut-off point to diagnose JHS is a score equal or greater than 4. This scoring system was originally set for epidemiological and research purposes and only explores the mobility of the joints, including only articular features of the syndrome and neglecting the extra-articular ones. The Brighton criteria were developed by Prof. Grahame in order to improve the Beighton scores by adding some extra-articular features. In 2000 Grahame developed the Brighton criteria to replace the Beighton criteria for the joint hypermobility syndrome [31]. According to these criteria, the syndrome diagnosis is made taking into account the Beighton score and also some other clinical manifestations associated with hypermobility. Nevertheless, the Hospital del Mar criteria were obtained after a multivariate analysis of margins from the original Beighton and Rotes scoring system. As opposed to the other criteria, this scale showed consistent indicators of reliability, internal consistency and predictive validity and provider evidence for using different scores for each gender [32]. See table 1 for details.

Besides this instruments, several self-assessment questionnaires have been developed to facilitate the diagnosis of the JHS [33]. Our group developed the Collagen Elasticity questionnaire to screen for JHS/hEDS see figure 2 for details. It is based on the Hakim and Grahame questionnaire [34] but includes pictures to facilitate the correct identification of the symptoms.

Despite the different sets of criteria and the variety of instruments, the JHS remains underdiagnosed and undertreated and the scientific community has highlighted the need to unify the criteria and the Gold standards to diagnose the JHS. In order to address this issue, the International Consortium on Ehlers-Danlos Syndromes & related Disorders has developed a

new checklist to diagnose the Hypermobile Ehlers Danlos Syndrome [35]. See figure 3 for details.

Table 1.Summary of the Beighton, Bulbena and Brighton criteria do diagnose JHS/hEDS

Beighton criteria
Evaluation of 5 joints Total Score: 0-9 Hypermobility: ≥ 5/9 *Assessment* -Forward flexion of the trunk with knees fully extended so that the palms of the hand rest flat* on the floor – one point -Hyperextension of the elbows beyond 10 degrees* – one point for each elbow -Hyperextension of the knees beyond 10 degrees* – one point for each knee -Passive apposition of the thumbs to the flexor aspect of the forearm* – one point for each hand -Passive dorsiflexion of the little fingers beyond 90 degrees* – one point for each hand.   

Bulbena criteria
Evaluation of 9 joints Total Score: 0--10 Hypermobility: ≥ 5/10 (women), ≥4/10 (men) **Assessment** Upper extremities 1. Passive apposition of the thumb to the flexor aspect of the forearm is at a distance <21 mm. 2. The passive dorsiflexion of the fifth finger is ≥ 90º. 3. The active hyperextension of the elbow is ≥10º. 4. External rotation of the shoulder ≥ 85º. Lower extremities. Supine position 5. The passive hip abduction can be taken to an angle of ≥ 85º. 6. Hypermobility of the patella. 7. Hypermobility of the ankle and foot. 8. Dorsal flexion of the toe is ≥90º Lower extremities. Prone position 9. Hyperflexion of the knee. Extra-articular 10. Ecchymosis

Brighton criteria
Major Criteria · A Beighton score of 4/9 or greater (either currently or historically) · Arthralgia for longer than 3 months in 4 or more joints Minor Criteria · A Beighton score of 1, 2 or 3/9 (0, 1, 2 or 3 if aged 50+) · Arthralgia (> 3 months) in one to three joints or back pain (> 3 months), spondylosis, spondylosis/spondylolisthesis. · Dislocation/ subluxation in more than one joint, or in one joint on more than one occasion. · Soft tissue rheumatism. > 3 lesions (e.g. epicondylitis, tenosynovitis, bursitis). · Marfanoid habitus (tall, slim, span/height ratio >1.03, upper: lower segment ratio less than 0.89, arachnodactyly [positive Steinberg/wrist signs]. · Abnormal skin: striae, hyper-extensibility, thin skin, papyraceous scarring. · Eye signs: drooping eyelids or myopia or antimongoloid slant. · Varicose veins or hernia or uterine/rectal prolapse.

Figure 2 Collagen Elasticity Questionnaire to diagnose the JHS.

COLLAGEN ELASTICITY QUESTIONNAIRE (C-SHC)

INSTRUCTIONS: Collagen is a protein that forms part of the skin, bones, tendons and connective tissue. This questionnaire gathers 7 simple questions to determine the degree of elasticity of the collagen fibers of your body. Please fill in the form and read the questions carefully, then circle one response (Yes / No).

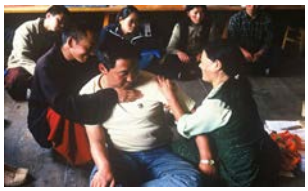
1. Can you now (or could you ever) place your hand flat on the floor without bending your knees?

2. Can you now (or could you ever) bend your thumb to touch your forearm?

3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits? (see examples).



4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?



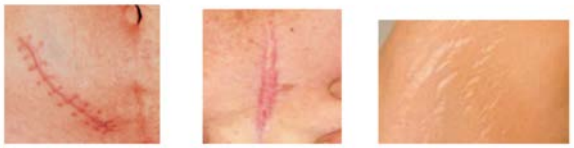
5. Do you consider yourself double-jointed?

Can you bend your elbow like this?

Have you disengaged your wrist when shaking hands?

Are you able to bend your fingers, elbows and knees like this?

6. Do you tend to have thick or wide scars? What about stretch marks? (see examples).



7. Would you bruise even without remembering being hit?

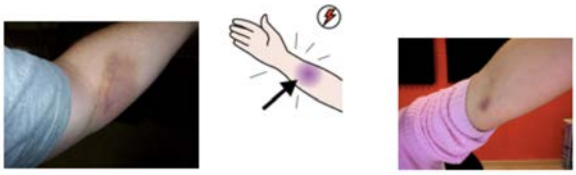


Figure 3. Checklist created by the International Consortium on Ehlers-Danlos Syndromes & related Disorders to diagnose the Hypermobile Ehlers-Danlos Syndrome

The International Consortium on Ehlers-Danlos Syndromes & Related Disorders
In Association with The Ehlers-Danlos Society

Diagnostic Criteria for Hypermobile Ehlers-Danlos Syndrome (hEDS)

This diagnostic checklist is for doctors across all disciplines to be able to diagnose EDS

Distributed by The Ehlers Danlos Society.

Patient name: _____ DOB: _____ DOV: _____ Evaluator: _____

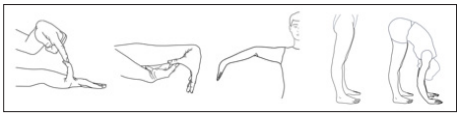
The clinical diagnosis of hypermobile EDS needs the simultaneous presence of all criteria, 1 ***and*** 2 ***and*** 3.

CRITERION 1 – Generalized Joint Hypermobility

One of the following selected:

- ☐ ≥6 pre-pubertal children and adolescents
- ☐ ≥5 pubertal men and woman to age 50
- ☐ ≥4 men and women over the age of 50

Beighton Score: _____/9



If Beighton Score is one point below age- and sex-specific cut off, two or more of the following must also be selected to meet criterion:

- ☐ Can you now (or could you ever) place your hands flat on the floor without bending your knees?
- ☐ Can you now (or could you ever) bend your thumb to touch your forearm?
- ☐ As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
- ☐ As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
- ☐ Do you consider yourself "double jointed"?

CRITERION 2 – Two or more of the following features (A, B, or C) must be present

Feature A (five must be present)

- ☐ Unusually soft or velvety skin
- ☐ Mild skin hyperextensibility
- ☐ Unexplained striae distensae or rubae at the back, groins, thighs, breasts and/or abdomen in adolescents, men or pre-pubertal women without a history of significant gain or loss of body fat or weight
- ☐ Bilateral piezogenic papules of the heel
- ☐ Recurrent or multiple abdominal hernia(s)
- ☐ Atrophic scarring involving at least two sites and without the formation of truly papyraceous and/or 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 (Walker sign) on both sides, (ii) positive thumb sign (Steinberg sign) on both sides
- ☐ Arm span-to-height ratio ≥1.05
- ☐ Mitral valve prolapse (MVP) mild or greater based on strict echocardiographic criteria
- ☐ Aortic root dilatation with Z-score >+2

Feature A total: _____/12

Feature B

- ☐ Positive family history; one or more first-degree relatives independently meeting the current criteria for hEDS

Feature C (must have at least one)

- ☐ Musculoskeletal pain in two or more 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

CRITERION 3 – All of the following prerequisites MUST be met

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 CTD (*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 toward a diagnosis of hEDS in this situation.
3. Exclusion of alternative diagnoses 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.* Bethlem myopathy), other hereditary disorders of the connective tissue (e.g. other types of EDS, Loeys-Dietz syndrome, Marfan syndrome), and skeletal dysplasias (*e.g.* osteogenesis imperfecta). Exclusion of these considerations may be based upon history, physical examination, and/or molecular genetic testing, as indicated.

2.3 ANXIETY AND THE ROLE OF THE CONNECTIVE TISSUE

Background

The relationship between the JHS and anxiety was an unexpected finding that our group first described in 1988 at the Hospital del Mar in Barcelona [36]. It really was a clinical observation rather than a pathophysiological reasoning and the reiterated coincidence of the two conditions prompted us to study this association in more detail. Prior to this study, there were some scattered observations in the literature pointing to this new direction. As mentioned above, Rotés observed a remarkable degree of nervous tension suffered by patients with hypermobility [22]. Besides this, there were some indirect references about the relationship between 'visceroptosis" and anxiety/phobias in the classical psychosomatic literature [37].

Bulbena et al. [38] conducted the first empirical case-control study where a sample of rheumatologic outpatients with JHS were assessed and 70% of hypermobile patients had some type of anxiety disorder, as compared to 22% in the controls. A second study [39] evaluated outpatients with new diagnoses of panic disorder and/or agoraphobia and found that JHS was present in approximately 70% of patients with anxiety disorders compared to 10% in the controls. García-Campayo et al. [40], also found a high prevalence of JHS (61.8%) among subjects suffering from panic disorders compared with 10.9% among healthy controls. A recent meta-analysis [41] revealed that people with JHS experience significantly greater perception and fear intensity and have higher probability of agoraphobia and panic disorders. These authors pointed out that current evidence is derived from Mediterranean adult populations and highlighted that more research should be done to study this association in other populations.

The only incidence study that evaluated the relationship between JHS and anxiety disorders was done in the general population with a 15 years follow up [42]. Cumulative incidence of panic/agoraphobia disorder was significantly higher in the JHS group (41.4%) with a relative risk of 22.3 [95% confidence interval (CI) 4.6–108.7, $P<0.0001$]. Incidence of social and simple phobia was also significantly higher in the JHS group and anxiolytic drug use was nearly fourfold higher among the hypermobile subjects. See details about those studies in table 2.

Table 2.Clinical studies regarding the association between joint hypermobility and anxiety

Study	Sample	Variables studied	Main Results
Bulbena 1988 [36] Bulbena 1993 [38] Spain	114 JH 59 controls	Anxiety: HAD-A EPQ, SCID III JH: Beighton	Significant association between JH and PD/A [OR 10.7 (4.8-23.8)] and simple phobia [OR 5.8 (2.0-16.20].
Martin-Santos 1998 [39] Spain	99 PD/A 99 psychiatric controls 64 medical controls	Anxiety; HAM A/D, SCID JH: Beighton Other: ECHO,	JH found on 67.7% of patients with anxiety [OR 18.6 (8.6-40.5)] (10.1% in psychiatric and 12.5% in medical control).
Lumley 1994 [43] USA	21 EDS III/JH 20 controls (other EDS)	Anxiety: HAM-A JH: EDS subtypes	EDS III higher scores on anxiety, depression, interpersonal sensitivity and pain.
Bulbena 1996 [44] Spain	99 PD/A 99 psychiatric controls 64 medical controls	Anxiety JH: Beighton Other: Quetelet index	Significant correlation between asthenic somatotype and PD/A [OR 2.23].
Pailhez 2014 [45] Spain	60 PD/A 60 controls	Other: somatotype, socio-demographic	Ectomorph somatotype independently related to JH [OR = 3.25, 95%; p = 0.008].
Benjamin 2001 [46] Israel	101 PD/A 30 healthy controls	Anxiety: NIMH, PSS, VAS 100mm JH: Beighton	JH = in both groups No association between carbon dioxide response and JH
Gulpek 2004 [47] Turkey	36 PD/A 42 PD/A + MVP 38 MVP	Anxiety: SCID IV / JH Beighton Other: ECHO	JH= 3 groups / PD/A higher JH MVP may affect JH prevalence in PD
Gulsun 2007 [48] Turkey	52 Thorax deformity 40 controls	Anxiety: SCID, HAM-A, JH: Beighton Other: Thorax diameter	21 patients with TD had JH + (40%) JH group had higher anxiety scores (especially PD). TD group higher anxiety scores (JH + and -)
Ercolani 2008 [49] Italy	JH 30 30 control Fibromyalgia 25 healthy control	Anxiety: DSM IV JH: Beighton Others: SCL-90-R, IBQ, SQ, FSF	JH group showed psychological distress and increased frequency and intensity of somatic symptoms
Garcia-	55 PD/A	Anxiety: PAS, STAI	Prevalence of JH in PD > than in

Campayo 2010 [50] Spain	55 psych. controls 55 Fibromyalgia controls 55 healthy control	JH: Beighton Other: SPPI	controls Prevalence of JH in PD 61.8% Significant correlation between PAS scores and Beighton criteria
De Wandele 2014 [51] Belgium	80 EDS-JH 11 classic EDS 7 vascular EDS 38 Fibromyalgia 43 controls	Anxiety: HADS JH: GHQ Others: ASP, QOL, SF 36, GHQ, fatigue checklist, Baecke Physical Activity	The total autonomic symptom burden was higher in EDS-HT (57.9 ± 21.57) than in the other groups but comparable to FM (53.8 ± 19.85)
Murray 2013 USA	466 adults with EDS JH	237 online survey	High frequency of chronic fatigue (82%), anxiety (73%), depression (69%), and fibromyalgia (42%) among EDS JH

HADS Hospital anxiety and depression scale; ASI: anxiety severity index; EPQ: Eysenck Personality questionnaires; SCID: Structured clinical interview for DSM; HAM: Hamilton anxiety and depression scale; ECHO: echocardiogram; EDS: Ehlers Danlos syndrome; NIMH: self-rating scale of mental symptoms; PSS: Panic symptom scale checklist; VAS: Visual analogue scale of anxiety; SCL-90: Symptom checklist 90 R; IBQ: illness behaviour questionnaire; SQ: Symptom questionnaire; FSF: Function symptoms frequency; PAS: Panic and agoraphobia scale; STAI: state trait anxiety inventory; SPPI: Standardized polyvalent psychiatric interview ; LSAS: Leibowitz social anxiety scale; ASP: autonomic symptom profile ; QOL: quality of life scale; SF-96: checklist of individual strength ; FSS: fear survey schedule ; GHQ: general health questionnaire ; BAI: Beck anxiety inventory ; SSAS Somatosensory amplification scale

Underlying mechanisms

While the association between anxiety disorders and JHS is well established, the underlying mechanisms are still unclear. Some biological hypotheses have been proposed to explain this association including genetic risks, interceptive sensitivity, somatosensory amplification, emotion processing variances, and autonomic nervous system dysfunction. In the area of genetics, one study found a cytogenetic anomaly (DUP-25) common to these two phenomena [52], although to date this study has not been replicated [53]. The perception and interpretation of physiological excitation plays a role in anxiety disorders [54, 55] and JHS subjects have more intense interoception [56] and somatosensory amplification [57]. Neuroimaging studies [58, 59] have shown significant emotion processing differences in JHS, which could in part explain the vulnerability for anxiety and other somatic symptoms.

Another important biological hypothesis is the autonomic nervous system dysfunction. Dysautonomia has symptoms that overlap with anxiety and JHS. Critchley et al. [60] extensively studied visceral inputs because of their influence on thoughts, feelings and behavior. Consistent Critchley ’s views, the Polyvagal Theory [61, 62] introduced a new perspective relating autonomic function to behavior that included an appreciation of autonomic nervous system as a “system,” the identification of neural circuits involved in the regulation of autonomic state that also influence responses to environmental stimuli and an interpretation of autonomic reactivity as adaptive within the context of the phylogeny of the vertebrate autonomic nervous system. Following this line of research, Porges developed the Body Perception Questionnaire (BPQ), an instrument to assess subjective experiences of body awareness and autonomic reactivity [63]. Compared to other scales that measure subjective experiences of body perception, the BPQ was developed with a foundation in the peripheral neural pathways that transmit bodily sensations to the brain, which provides valuable information about the reactivity of autonomically-regulated organs.

3 AIMS AND HYPOTHESIS

The global aim of this thesis is to further explore the association between anxiety and JHS/hEDS and the underlying mechanisms behind this association and also to study the full range of psychopathology associated with the JHS/hEDS.

The study 1 and 2 are review papers and aimed to review the published literature regarding the association between the JHS/hEDS and the related psychopathology with a special emphasis on anxiety disorders. The first review also reviewed the therapeutic dimension and offered future directions in this field. For the purpose of this thesis we included specific aims and hypothesis only for the observational studies described below.

3.1 JOINT HYPERMOBILITY IS ALSO ASSOCIATED WITH ANXIETY DISORDERS IN THE ELDERLY POPULATION

Main Aim

- To identify if JHS/hEDS is associated with anxiety disorders in elderly general population.

Specific Aims

- To describe anxiety and depression in elderly general population, using both clinical and somatic instruments.
- To study the association between anxiety (both clinical and somatic) and JHS/hEDS in this age range.
- To clarify if fears are associated with JHS/hEDS in this age range.
- To explore the association between depression and JHS/hEDS and in this population.

Hypothesis

- The prevalence of JHS/hEDS in this population will be <20%.
- Females will be more hypermobiles than males in a ratio 3:1.
- JHS will be associated with anxiety in the elderly.
- Subjects with JHS will have greater fears and somatic complaints.

3.2 BODY PERCEPTION IN A SAMPLE OF NONCLINICAL YOUNGSTERS WITH JOINT HYPERMOBILITY

Main Aim

- To describe the body perception profiles in JHS/hEDS.

Specific Aims

- To study body perception and the functioning of the Autonomic Nervous system using the Body Perception Questionnaire in JHS/hEDS.
- To define the frequency of autonomic related illnesses in a sample of nonclinical youngsters.
- To compare body perception between JHS/hEDS and non-hypermobile subjects
- To explore the relationship between JHS/hEDS and autonomic related illnesses.

Hypothesis

- The prevalence of JHS/hEDS in this sample will be greater than 20%.
- Females will be more hypermobiles than males in a ratio 3:1
- Participants with JHS/hEDS will have greater body perception.
- Subjects with JHS/hEDS will have greater frequency of self-reported anxiety and eating disorders.
- Subjects with JHS/hEDS will have higher frequency of autonomic related illnesses.

4 METHODS

4.1 STUDY 1 & 2: PSYCHIATRIC AND PSYCHOLOGICAL ASPECTS IN THE EHLERS-DANLOS SYNDROMES & JOINT HYPERMOBILITY, ANXIETY AND PSYCHOSOMATICS: TWO AND A HALF DECADES OF PROGRESS TOWARD A NEW PHENOTYPE.

Both articles are review papers. The paper entitled “Psychiatric and psychological aspects in the Ehlers-Danlos syndromes” was part of the 2016 International Consortium on the Ehlers-Danlos Syndromes. The working group on the psychological and Psychiatric aspects of the Ehlers-Danlos Syndromes was composed of well-respected international clinician-researchers in the area of psychopathology with special interests in Ehlers-Danlos syndromes. The consensus about management guidelines was obtained after all authors completed their contributions and reviewed the manuscript on three separate occasions to ensure general agreement by all the authors. The other article entitled “Joint hypermobility, anxiety and psychosomatics: two and a half decades of progress toward a new phenotype” is a book chapter of the book “Clinical Challenges in the Bio-psychosocial Interface” (Editors Prof. Richard Balon and Prof. Thom Wise).

Literature searches for both articles were conducted using the main electronic databases including the Cochrane Library, Informit, PsycINFO, PubMed, and Scopus. The main search terms used were “joint hypermobility syndrome”, “joint hyperlaxity”, “anxiety”, and each separate psychiatric diagnostic category. Studies were included if they were published until September 2016, either in English or Spanish, if they reported any psychiatric conditions associated with joint hypermobility. Reference lists of the obtained articles were also screened for potentially relevant papers.

4.2 STUDY 3: JOINT HYPERMOBILITY IS ALSO ASSOCIATED WITH ANXIETY DISORDERS IN THE ELDERLY POPULATION

Study details and sample characteristics

The study is part of a large cross sectional epidemiological study of a rural town in Spain (Portbou, Girona, Spain). Subjects that were 60 y/o or older were included after the study procedures was fully explained and the informed consent was obtained. The presence of dementia or cognitive impairment, psychotic comorbidities, severe physical (particularly rheumatologic) disease, severe heritable connective tissue disease and age under 60 y/o were the exclusion criteria. The participation of the study was voluntary with no monetary reward and the study was approved by the local ethic committee.

Instruments

Socio-demographic variables were obtained through direct interview. Clinical measurements were obtained using the following instruments:

- The structured diagnostic interview (SCID) was used to assess anxiety and mood disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria (SCID IV) [64]. Major depression disorder (MDD), dysthymia, generalized anxiety disorder (GAD), panic disorder (PD), agoraphobia, specific phobia and social phobia past year estimated prevalence's were assessed by a trained SCID researcher blind to the Joint hypermobility status. Clinical records were also reviewed by an independent psychiatrist blind to the research information to complete the diagnostic information obtained in the interview.
- The JHS was evaluated by a trained rater using Hospital del Mar criteria, which is a ten-point clinical scale which uses a different cut off point for men and women (3/4 and 4/5) [32]. Because of the age range, a lower cut off range (1 point lower) was applied to take into account the loss of agility seen in this type of population (2/3 males and 3/4 females).

- Dimensional measurements of anxiety symptoms were evaluated using the State-Trait Anxiety Inventory (STAI) [65].
- Fears were evaluated with the modified Wolpe Fear Survey Schedule (mFSS), which is a self-reporting questionnaire that contains a list of the 100 most commonly feared things and situations that are then rated in regard to the intensity of the fear. A modified and validated Spanish version was used [66].
- To increase the panic screening, we also used the four autonomic questions proposed by Katon developed in 1987 [67] (1. "Do you ever have sudden episodes of rapid heartbeat or feeling like your heart is pounding?" 2. "Do you ever have sudden episodes of lightheadedness or feeling faint? 3. "Do you ever have sudden episodes of sweating, hot flashes, or trembling?" 4. "Do you every have sudden episodes of chest tightness or a feeling of smothering or not being able to get enough air to breath?" and the panic detection screen question proposed by the National Institute of Mental Health Diagnostic Interview Schedule (DIS) [68] ("Have you ever had a spell or attack when suddenly you felt frightened, anxious or very uneasy in situations when most people would not be afraid?")
- Additionally, the General Health Questionnaire-28 [69] was used to determine the likelihood of the presence of psychopathology and somatic conditions.

Statistical analysis

Descriptive statistics were used to report the frequencies, means and standard deviations. Continuous variables were reported as means and standard deviations (SD) and categorical variables were reported as % (n). Student's t tests and ANOVA were used when comparing for continuous data and $\chi 2$ tests for categorical data. Statistical significance was determined by two-tailed $p<0.05$. Multiple logistic regression analyses models were used to examine the predictive value of JHS for the diagnosis of anxiety disorders in the sample. All statistical analyses were made using the SPSS – IBM version 22 for Macintosh.

4.3 STUDY 4: BODY PERCEPTION IN A SAMPLE OF NONCLINICAL YOUNGSTERS WITH JOINT HYPERMOBILITY

Study details and sample characteristics

In this study, we evaluated a sample of nonclinical youngsters to assess JHS in relation to the level of awareness of body processes, the subjective experience of autonomic nervous system reactivity, and the frequency of autonomic related illnesses. This cross-sectional study was conducted in a high school in Barcelona (Spain) and a total of 117 subjects (33 males (28.2%) and 84 females (71.7%) with ages ranging from 16-18 y/o were included in the study. All the interested students were selected as eligible and no exclusion criteria were applied. Participation of the study was voluntary without any economic compensation and the informed consent from participants was obtained after the study procedures were fully explained.

Instruments

Socio-demographic data was obtained through a questionnaire (including visits to the psychiatrist or the psychologist). Among the sample, the mean age was 16.96 (SD± 0.87) years old and 41 (35%) subjects were from 11th grade and 76 (65%) from 12th grade and all of them were Caucasians. In terms of visits to a mental health professional, 32 subjects (27.35%) admitted to seeking mental health help and 85 (72.65%) denied it.

- The JHS was screened with the self-reported Screening Questionnaire for Collagen condition and Hypermobility's assessment (SQCH) [33]. This questionnaire has adequate clinimetric properties and has been validated for clinical use and cut-off scores to diagnose JHS are set at ≥3/7.
- Body perception was evaluated using the Spanish version of the Body Perception Questionnaire (BPQ) [63]. It has a total of 5 dimensions including body awareness (45 items), stress response (10 items), autonomic nervous system (ANS) reactivity (27 items), stress style (12 items, subgroup 1 and 2) and health history inventory (27 items). All ratings except for the Health History Inventory dimension are made on a five-point ordinal scale

spanning never (0), occasionally (1), sometimes (2), usually (3), and always (4). The health history inventory also used a five-point ordinal scale but slightly different spanning never (0), mild (1), moderate (2), severe (3) and debilitating (4). Total final score of each dimension is showed as the mean score of each category. The health history inventory included some autonomic-related illnesses including migraine headaches, gastric distress or digestive problems, arthritis, hypertension, hopeless, unhappiness, clinical depression, bulimia, anorexia, obesity, asthma, endocrine problems (e.g., thyroid, adrenal, or gonadal hormone dysfunction), eczema, edema, back problems, diabetes, epilepsy, cancer, hypoglycemia, heart disease, stroke, gastric & duodenal ulcers, psychiatric disorders, pneumonia, heart attack, motion sickness. The following are only for women only; premenstrual syndrome, severe menstrual cramps and post-partum depression.

Statistical analysis

Descriptive statistics were used to report frequencies, means and standard deviations (SD). The Student tests and ANOVA were used for continuous data and $\chi 2$ tests for qualitative data. Statistical significance was determined by two-tailed $p<0.05$. All statistical analyses were conducted with SPSS – IBM version 22 for Macintosh.

5 RESULTS

5.1 STUDY 1 & 2: PSYCHIATRIC AND PSYCHOLOGICAL ASPECTS IN THE EHLERS-DANLOS SYNDROMES & JOINT HYPERMOBILITY, ANXIETY AND PSYCHOSOMATICS: TWO AND A HALF DECADES OF PROGRESS TOWARD A NEW PHENOTYPE.

As stated earlier, the relationship between JHS/hEDS and anxiety disorders has been widely explored during the past 30 years and current literature supports a solid association between these two variables [70]. The clinical studies that evaluated the relationship between these 2 variables were described in the introductory section. However, several studies done non-clinical samples have also confirmed the strong association between these variables, see table 3 for details. Also, a recent meta-analysis [41] revealed that people with JHS/hEDS experience significantly greater perception and fear intensity and have higher probability of agoraphobia and panic disorder. These authors pointed out that current evidence is derived from Mediterranean adult populations and highlighted that more research should be done to study this association in other populations.

Table 3. Study 1&2; Non-clinical studies that evaluated the relationship between JHS/hEDS and anxiety

Study	Setting	Sample	Variables studied	Main Results
Bulbena 2004 [28] Spain	General population	1305 subjects	Anxiety: JH: Beighton MVP	Significant association between JH and PD/A [OR 10.7 (4.8-23.8)] and simple phobia [OR 5.8 (2.0-16.20].
Bulbena 2004 [29] Spain	Medical department	526 subjects	Anxiety: STAI JH: Hospital del Mar	Males and females with JHS significantly higher trait anxiety scores ($p<0.001$). Both trait and state anxiety showed significant correlations with JHS (Spearman's rho, 0.10–0.16; $P<0.05$).
Bulbena 2006 [30] Spain	General population	1305 subjects	Anxiety: FSS JH: Beighton	JH group higher fear and intensity of fears. The association of JH and phobic anxiety might represent a susceptibility factor for these anxiety conditions.
Baeza-Velasco 2009 [31] France	Internet survey in tall subjects	158 subjects	Anxiety: LSAS JH: Beighton	High rate of JH and social phobia in tall subjects JH greater social phobia symptoms.
Baeza-Velasco 2010 [32] Chile	University students	50 JH 50 Control	Anxiety: HADS, LSAS JH:	JH group had higher use of antidepressants and anxiolytics compared to the controls. They also exhibited greater anxiety background, anxiety symptoms and psychosomatic complaints
Baeza-Velasco 2011 [33] France	University students	365 subjects	Anxiety: HADS, LSAS JH: Beighton	JH was associated with higher levels of somatosensory amplification as well was higher scores in depression and general anxiety females.
Pailhez 2011 [34] Spain	High school students	150 subjects	Anxiety: FSS JH: Hakim Others: chocolate rate	Higher fear scores in JH Frequency of chocolate intake higher in JH

Bulbena 2011 [35] Spain	General population	137 subjects followed 15 years	Anxiety: SCID, STAI, ASI, FSS JH: Beighton, Bulbena Other: GHQ	JH RR: PD/A: 22 (5-109) Social phobia: 6.5 (1.7-24.2) Simple phobia: 3.3 (1.1-9.6) GAD: 2.9 (0.97-8.6). JH scored higher in social dysfunction subscale and other use of anxiolytics; Concordance between Beighton scale and Brighton (Kappa=0.91) and Hospital del Mar (Kappa=0.61).
Baeza-Velasco 2014 [40] France	College students	305 females	Anxiety: STAI JH: S-CHQ Other: SA	More tobacco and alcohol if JHS JH higher scores on state anxiety.
Eccles 2012 [44] UK	General population	72 healthy volunteers	Anxiety: BAI JH: Beighton Other: Brain MRI, PBPQ	Amygdala volume greater in JH JH higher scores in interoceptive sensitivity an anxiety. JH linked to brain center implicated with emotions and physiological responses,

HADS Hospital anxiety and depression scale; ASI: anxiety severity index; EPQ: Eysenck Personality questionnaires; SCID: Structured clinical interview for DSM; HAM: Hamilton anxiety and depression scale; ECHO: echocardiogram; EDS: Ehlers Danlos syndrome; NIMH: self-rating scale of mental symptoms; PSS: Panic symptom scale checklist; VAS: Visual analogue scale of anxiety; SCL-90: Symptom checklist 90 R; IBQ: illness behaviour questionnaire; SQ: Symptom questionnaire; FSF: Function symptoms frequency; PAS: Panic and agoraphobia scale; STAI: state trait anxiety inventory; SPPI: Standardized polyvalent psychiatric interview ; LSAS: Leibowitz social anxiety scale; ASP: autonomic symptom profile ; QOL: quality of life scale; SF-96: checklist of individual strength ; FSS: fear survey schedule ; GHQ: general health questionnaire ; BAI: Beck anxiety inventory ; SSAS Somatosensory amplification scale.

Mood disorders: Some studies examined the relationship between mood disorders and JHS/hEDS but research on this area is significantly smaller compared to anxiety disorders. Two studies [71, 72] explored depressive disorders in JHS/hEDS subjects but no differences were found when comorbid anxiety was controlled for. In contrast, Pasquini [73] observed a higher rate of depressive symptoms in JHS/hEDS patients compared to controls. Other studies also revealed higher depressive symptoms in individuals with joint hypermobility (JH) without a known diagnosis of JHS/hEDS [57] [74]. The meta-analysis of Smith et al. [41] concluded that people with JHS/hEDS commonly exhibit more anxiety and depressive symptoms. Hershenfeld et al. [75] found 42.5% prevalence of psychiatric disorders (especially depression and anxiety) in a retrospective sample of JHS/hEDS subjects. Therefore, some preliminary evidence suggests higher rates of depressive symptoms among JHS/hEDS, especially when comorbid anxiety is present.

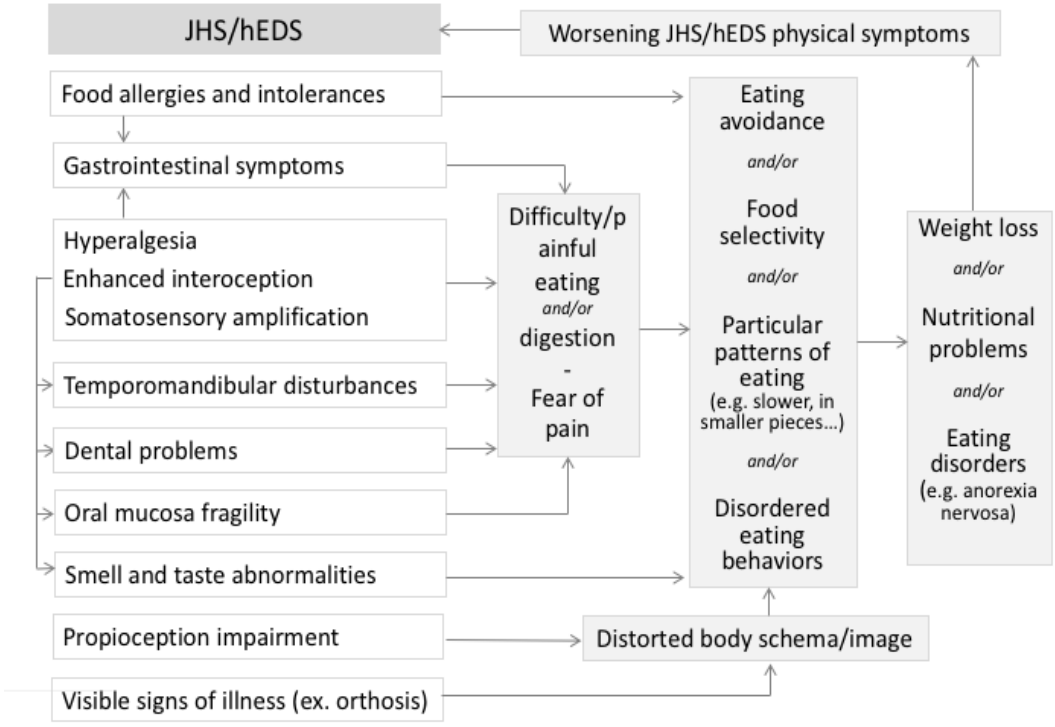
Personality disorders: The evidence in the field of personality disorder is very scarce and to date there is only one study published about it. Pasquini et al. [73] observed that subjects with JHS/hEDS have a 5.8 relative risk of having a personality disorder, particularly anxious obsessive-compulsive personality disorder. Although this is in line with prior research studies that support a strong relationship between anxiety and JHS/hEDS, these results should be interpreted with caution due to the lack of large, well-designed studies in this field.

Addictions: Most of the research about addiction in JHS/hEDS focused on substances (alcohol and tobacco mainly) and there are no studies about other addiction dimensions like gambling or sex addiction. Carlsson [76] et al. found significantly higher joint hypermobility scores among female alcoholic patients, but did not fully evaluate for the JHS/hEDS in these patients. Interestingly, in that study they proposed a link between hormonal dysregulation and increased joint laxity. Lumley et al. [43] reported that in a sample of EDS patients (N=48; including adults and children and multiple types), 12% had a history of alcohol or illicit drug use although the type of illicit substance was not specified. Since chronic pain was one of the major psychological stressors in that study, it would be interesting to know if there was a misuse of pain medications as well. Regarding tobacco addiction, Carbone et al. [77] studied the bone density

in JHS/hEDS and found that the control group smoked more tobacco and were taller compared to the JHS/hEDS group, which is not consistent with other findings that showed that patients with JHS/hEDS have a tendency towards the ectomorph phenotype (thin and tall) and also that people with hEDS smoke more cigarettes. A longitudinal study found smokers had significantly higher joint hypermobility scores [78] which was consistent with prior studies. Additionally, coping with distress is frequently cited as a reason for the higher tobacco and alcohol use as both substances are known to reduce anxiety.

Eating disorders: Most studies seem to point towards a relationship between the ectomorph somatotype (linear, thin, and usually tall) and the JHS/hEDS [78], with higher rates of restrictive or compensatory eating disorders such as anorexia or bulimia. Some case reports described a co-occurrence of EDS and eating disorders such as anorexia nervosa (AN) [79, 80] although the type of EDS was not specified in the reports. Goh et al. [81] hypothesized that since there is symptom overlap seen anorexia and joint hypermobility such as gastrointestinal symptoms, orthostatic intolerance and fatigue associated syndromes, joint hypermobility is a possible indicator of a familial disorder of connective tissue elasticity which potentially plays a causal role in the development of the eating disorder. Recently, Baeza-Velasco et al. [82] proposed a model of eating disorders in JHS/hEDS that provided some light about this phenomenon. The authors hypothesized that both articular and extra-articular features play a role in developing and maintaining these eating patterns, see figure 4 for details.

Figure 4. Model of eating disorders in JHS/hEDS described by Baeza-Velasco



Psychosis: There are some articles addressing the relationship between JHS/hEDS and schizophrenia. Bulbena et al. [83] studied 124 patients with schizophrenia with and without comorbid JHS/hEDS and found joint hypermobility was markedly more frequent among the schizophrenic-panic/phobic cluster (62.1%) ($p<0.0001$). Similarly, Bulbena et al. [84] found that individuals with comorbid schizophrenia JHS/hEDS had higher rates of phobia/panic anxiety and more positive symptoms as well, and postulated that joint hypermobility could be a clinical marker for this phenotype in schizophrenia. In a third case control study (schizophrenic patients vs healthy controls) done by the same group evaluating the somatotype in schizophrenia, JHS/hEDS had comparable rates between the groups but there was a tendency towards positive association between anxiety - joint hypermobility and anxiety-ectomorphism [85]. A case report by Sienaert et al. [86] described a case where a patient with comorbid schizoaffective disorder and classical EDS received electroconvulsive therapy , although it is unclear if the patient met diagnostic criteria for classical EDS.

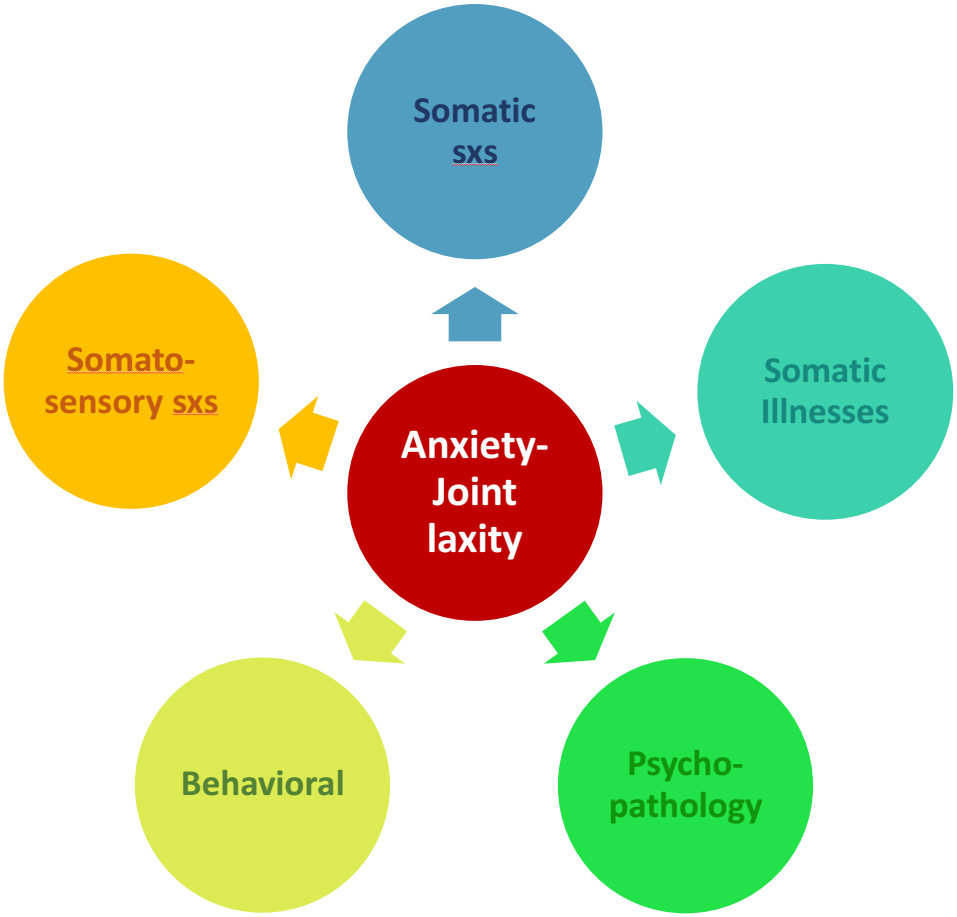
Neurodevelopmental disorders: This is a burgeoning area of research that has developed over the recent years which seems to indicate a degree of co-occurrence of JHS/hEDS and some neuro-developmental disorders including attention-deficit/hyperactivity disorders (ADHD), developmental coordination disorder (DCD) and autism spectrum disorder (ASD). In the area of ADHD, Eccles et al. [87] found that adults with ADHD had higher rates of joint hypermobility and symptoms of autonomic dysfunction compared to healthy controls. Another study, done by Harris et al. [88] that was published as a letter to the editor, found that the great majority (99%) of children with ADHD in this sample had joint hypermobility, although this results should be interpreted with caution as it is based on clinical observations with no clear methodology reported. Similarly, Hollertz et al. [89] reported high co-occurrence of EDS and ADHD based on an observational study. Other authors such as Dogan et al. [90] and Shiari et al. [91] did matched case control studies and found that joint hypermobility was significantly higher in the ADHD group as well as anxiety compared to healthy controls. Concerning DCD, Kirby [92] reported that children with DCD have more symptoms associated with JHS/hEDS including joint hypermobility, pain and autonomic dysfunction compared to asymptomatic typically developing

children. Jelsma et al. [93] found significantly higher mean scores of joint hypermobility in the DCD-group as compared to age-matched, typically developing children. Ghibellini et al. [94] suggested that the relationship between JH and DCD may be due to poor proprioception in hypermobile children. No articles are published regarding the relationship between ASD and JHS/hEDS but a few have looked at the prevalence of JH in ASD. Shetreat-Klein et al. [95], did a matched case control study and found that ASD children have greater mobility of joints and more gait abnormalities compared to healthy controls. However, this study had a relatively small sample and excluded children with overt neurological problems, which may not be an accurate representation of the ASD population. Also, few case reports also highlighted the comorbidity ASD – joint hypermobility [96],[97],[98], but further studies need to explore the possible association between these two variables.

The Neuro-Connective Phenotype

Although there is increasing proof of somatic comorbidity in the major psychiatric conditions, present psychiatric classifications are not yet including specific psychiatric illnesses associated to medical conditions other than organic dementias and secondary psychiatric conditions. However, the overwhelming data on clinical comorbidity (both somatic and psychiatric) require new nosotaxic approaches. Following the accumulated evidence on this topic over the past 30 years, our group described the “Neuro-connective phenotype” on the basis of the collected genetic, neurophysiological, neuroimaging and clinical data. The core of the phenotype includes the “Anxiety-Collagen hyperlaxity” association and has 5 dimensions that allow minor overlap (somatic symptoms, somatic illnesses, psychopathology, somatosensory symptoms, and behavioral) see figure 5 for details. Each of the following five dimensions includes features that may be present at different degrees with individual variations.

Figure 5. The Neuro-connective phenotype



- Behavioral Dimensions are patterns of defensive mechanisms that are often identifiable at the extreme of a continuous axis (i.e. fight/flight, restriction (avoidance)/dependency
- Somatic symptoms include dysautonomia, asthenic somatotype, "blue "sclera, "easy bruising", eczemas, dyskinesia, dislocations, prolapses and hypertrophic scars
- Somatic Conditions: irritable bowel syndrome, dysfunctional esophagus, chemical sensitivities, dizziness, fatigue, fibromyalgia, dynias, hypothyroidism, asthma, migraines, temporomandibular dysfunction and food intolerances.
- Psychopathology: increased interoception, exteroception, decreased proprioception, anticipatory anxiety, high sensitivity to loss, phobias, depression, eating and neuro-developmental disorders, anxious type personality disorders (Obsessive compulsive personality disorder).
- Somato-sensory symptoms include increased olfactory sensitivity, eye-contact difficulty, selective photophobia, dyspnea, dysphagia, choking, palpitations, and joint pain and enhanced sensitivity to weather and chemicals, particularly psychotropic drugs.

Therapeutic approaches

Although no specific studies about psychopharmacologic treatment for hEDS have been published yet, there is evidence that JHS/hEDS patients take more anxiolytics than the counterpart. The only longitudinal study that studied this association found that the overall use of psychotropic drugs was 41.4% in hypermobile subjects as opposed to 13.9% in the control group (OR: 4.38 CI 95% 1.8- 10.9) [42].

High levels of anxiety and depression are frequent in JHS/hEDS [41] and it has been shown that negative emotions may increase the experience of pain [99]. Celleti et al. [100] observed that patients with a JHS/hEDS had high scores of kinesiophobia. JHS/hEDS patients also have hyperalgesia [101], enhanced interoception [56] and a tendency towards a somatosensory amplification [57]. These aspects related to increased perception and/or reduced tolerance of pain [102][103] might influence the pain experience. In fact, taking into account that these patients have several body complaints, further studies should explore the role of meditative therapies like yoga or Pilates that combine relaxation techniques, stretching, and physical exercises.

Dysfunctional coping strategies have been also associated in patients with joint hypermobility [104]. However, there are no studies exploring the coping strategies in JHS/hEDS and the psychological aspects of pain perception merits more research to develop treatments programs. Some pilot cognitive behavioral therapy (CBT) experiences have been developed and suggested that CBT is valuable in the pain management of JHS/hEDS patients [105].

5.2 STUDY 3: JOINT HYPERMOBILITY IS ALSO ASSOCIATED WITH ANXIETY DISORDERS IN THE ELDERLY POPULATION

The study sample included 108 subjects, fifty-nine females (55%) and forty-nine males (45%) with no age differences (67.4y/o vs. 68.5y/o; t= 1.029; p= 0.306), 19,4% did work outside their home, 15.7% had been visiting a psychiatrist in the last year (22% of women and 8.2% men; X^2 3.88; p= 0.0664) and 22.2% had taken psychotropic drugs (14.3 % of men and 28.8% women; X^2 3.27; p= 0.103), see details in table 4.

Table 4. Study 3; Differences in Socio-demographic variables in the sample

	Male	**Female**	***p*-value**
N = 108	49 (45%)	59 (55%)	-
Age	68.5 y/o	67.4 y/o	0.306
Psychiatrist visit past year	8.2%	22%	0.064
Psychotropic drugs	14.3%	28.8%	0.103

Twenty-one percent of the sample met Hospital del Mar criteria for Joint hypermobility (32.3 % of women and 8.2% men; X^2 9.23, p= 0.004). Since we were interested in studying the association between anxiety and the joint hypermobility syndrome, several variables were compared between the hypermobile group and the non-hypermobile one.

Subjects with JH scored significantly higher in both anxiety state (F= 5.53; p= 0.02) and trait (F= 4.68; p= 0.03), GHQ 28 (F= 6.29; p= 0.01) and also scored higher in the total score of the modified Wolpe Fear Survey Schedule although this did not reach statistical significance (F= 2.12; p= 0.15). Find complete information in table 5.

Table 5. Study 3; Clinical rating differences between JHS and non JHS groups (=significant)*

Variable	JHS	non JHS	F	*p*- value
STAI- State	30 (±4.6)	26.2 (±7.2)	5.53	0.02*
STAI- Trait	30.7 (±5.3)	27.8 (±5.6)	4.67	0.03*
GHQ A (somatic symptoms)	1.70 (±2.3)	1.00 (±1.8)	2.28	0.13
GHQ B (anxiety/insomnia)	2.13 (±1.9)	1.31 (±1.9)	3,16	0.07
GHQ C (social dysfunction)	0.93 (±1.5)	0.87 (±1.2)	0.03	0.86
GHQ D (depression)	0.74 (±1.7)	0.64 (±1.3)	0.19	0.76
GHQ TOTAL	22.7 (±5.5)	18.6 (±7.2)	6.29	0.01*
Modified Wolpe Fear Score	134.6 (±51.5)	116.6 (±50.3)	2.12	0.15

We also compared the panic screen question of the DIS with the four autonomic questions proposed by Katon to increase the detection of panic between groups. Two questions were answered significantly different when comparing hypermobiles with non-hypermobiles (**"**Have you ever had a spell or attack when all of the sudden you felt frightened, anxious, or very uneasy in situations when most people would not be afraid?" (*p*=0.019) and "Have you ever had sudden episodes of palpitations or heart pounding?" (*p*=0.028)). However, despite the JHS group scored higher in the remaining questions, no significant differences were found between the two groups, details in table 6.

Table 6. Study 3; Panic screen (DIS and Katon (K)) scoring differences between groups (=significant)*

Panic Screen question	JHS	No JHS	*p*-value
Suddenly feeling frightened anxious, uneasy in situations where others do not? (DIS)	26.1%	7.1%	0.019*
Sudden palpitations or heart pounding? (K)	60.9%	32.9%	0.028*
Sudden lightheadedness or feeling faint? (K)	21.7%	15.3%	0.530
Sudden episodes of sweating, hot flashes, or trembling? (K)	26.1%	12.9%	0.192
Sudden episodes of chest tightness or not being able to get enough air? (K)	26.1%	20.0%	0.570

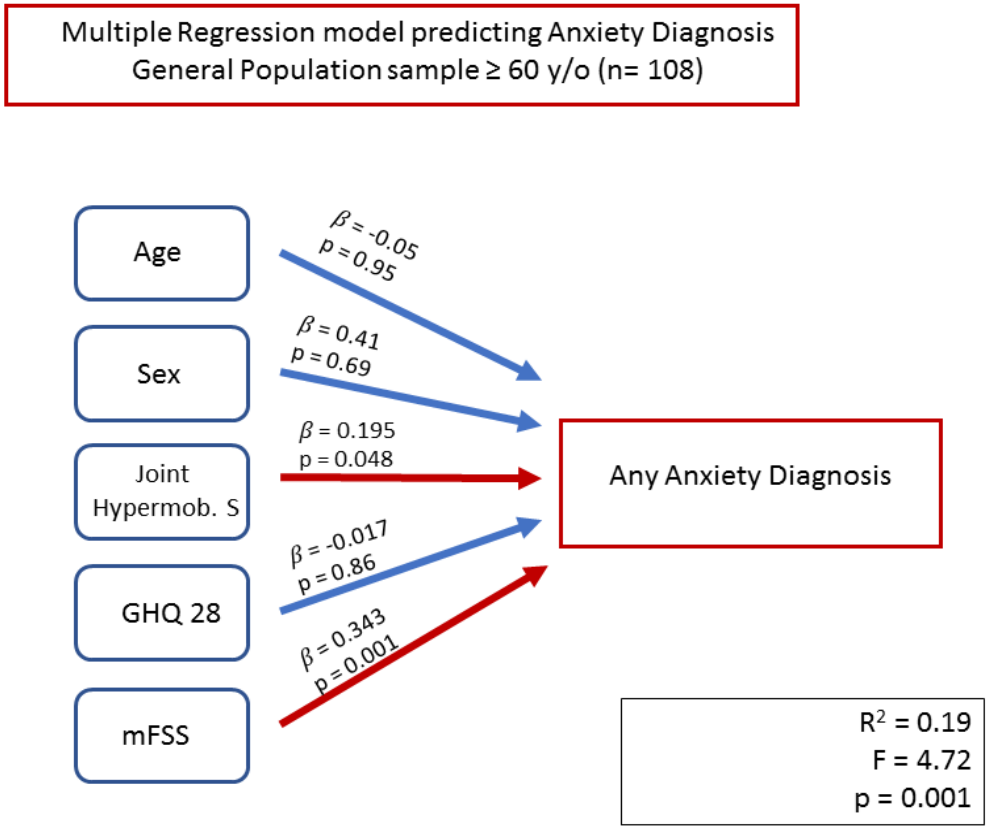
Concerning diagnoses, 14.8% of the sample had past year diagnosis of mood (Major depression 8.3% and dysthymia 6.48%) and 16.7% of the sample had past year diagnosis of anxiety disorders (7.4% GAD, 3.7% Panic or Agoraphobia, 2.8% Social phobia, 2.8% Specific phobia). Comorbidity between mood and anxiety disorders was frequent; more than half (55.6%) subjects with anxiety had comorbid depression, and almost seventy percent of the patients with depression (68.7%) were diagnosed also with anxiety disorders. When comparing hypermobiles and non-hypermobiles, the JHS group had higher past year prevalence of anxiety (34.8% vs 11.8%; X^2=6.90; p= 0.02) and depression (30.4% vs 10.6%; X^2=5.65; p= 0.041). When JHS patients with depression and comorbid anxiety were excluded from the analysis, no significant differences were found between groups for depression (13.0% vs 2.4%; X^2=4.68; p= 0.06). However, when anxiety without any comorbid depression was compared between groups, the JHS group had significant higher rates of anxiety disorders (21.7% vs. 3.52%, p=0.01), highlighting the solid correlation between anxiety and JHS, full information in table 7.

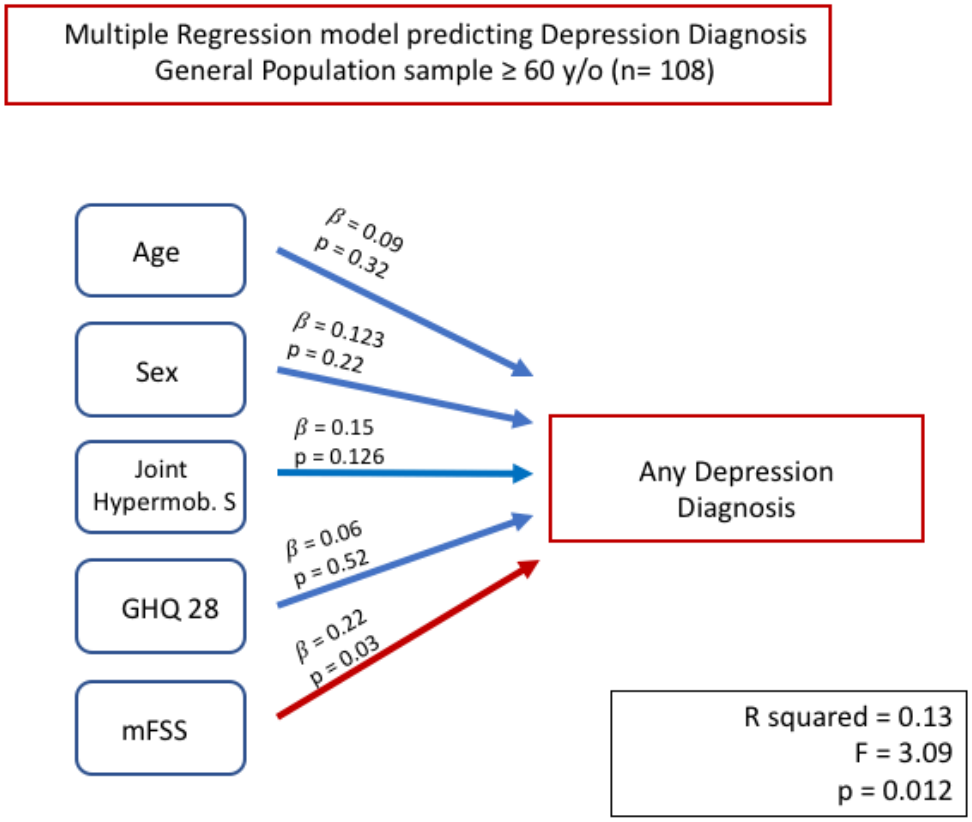
Table 7. Study 3; Past year prevalence of anxiety and depression differences between groups (=significant).*

Diagnosis	JHS	Non JHS	*p*-value
Anxiety with comorbid depression	34.8%	11.8%	0.02*
Depression with comorbid anxiety	30.4%	10.6%	0.04*
Anxiety without comorbid depression	21.7%	3.52%	0.01*
Depression without comorbid anxiety	13.0%	2.4%	0.06

A multiple regression analysis was built to identify the predictive value of JHS for anxiety and depression in this sample, which was taken as the predicted variable respectively, see figure 6 for details. Besides the JHS, we included as predictors GHQ-28, the modified Wolpe mFSS, age and sex. Both Joint hypermobility (β=0.196; *p*= 0.04) and the mFSS (β= 0.34; *p*= 0.001) were significantly associated with the diagnosis of anxiety disorders (r^2= 188; *p*=0.001). However, it did not reach significance for age, sex and GHQ-28. The same model was built with depression as the predicted variable and it was also significant (r^2= 132; *p*=0.01) but only the mFSS reached significance (β = 0.21; *p*= 0.03).

Figure 6. Study 3; Multiple regression model predicting AD anxiety and depression in a sample of elderly patient.




Multiple Regression model predicting Depression Diagnosis
General Population sample ≥ 60 y/o (n= 108)
Age
Sex
Joint Hypermob. S
GHQ 28
mFSS
β = 0.09
p = 0.32
β = 0.123
p = 0.22
β = 0.15
p = 0.126
β = 0.06
p = 0.52
β = 0.22
p = 0.03
Any Depression Diagnosis
R squared = 0.13
F = 3.09
p = 0.012

5.3 STUDY 4: BODY PERCEPTION IN A SAMPLE OF NONCLINICAL YOUNGSTERS WITH JOINT HYPERMOBILITY

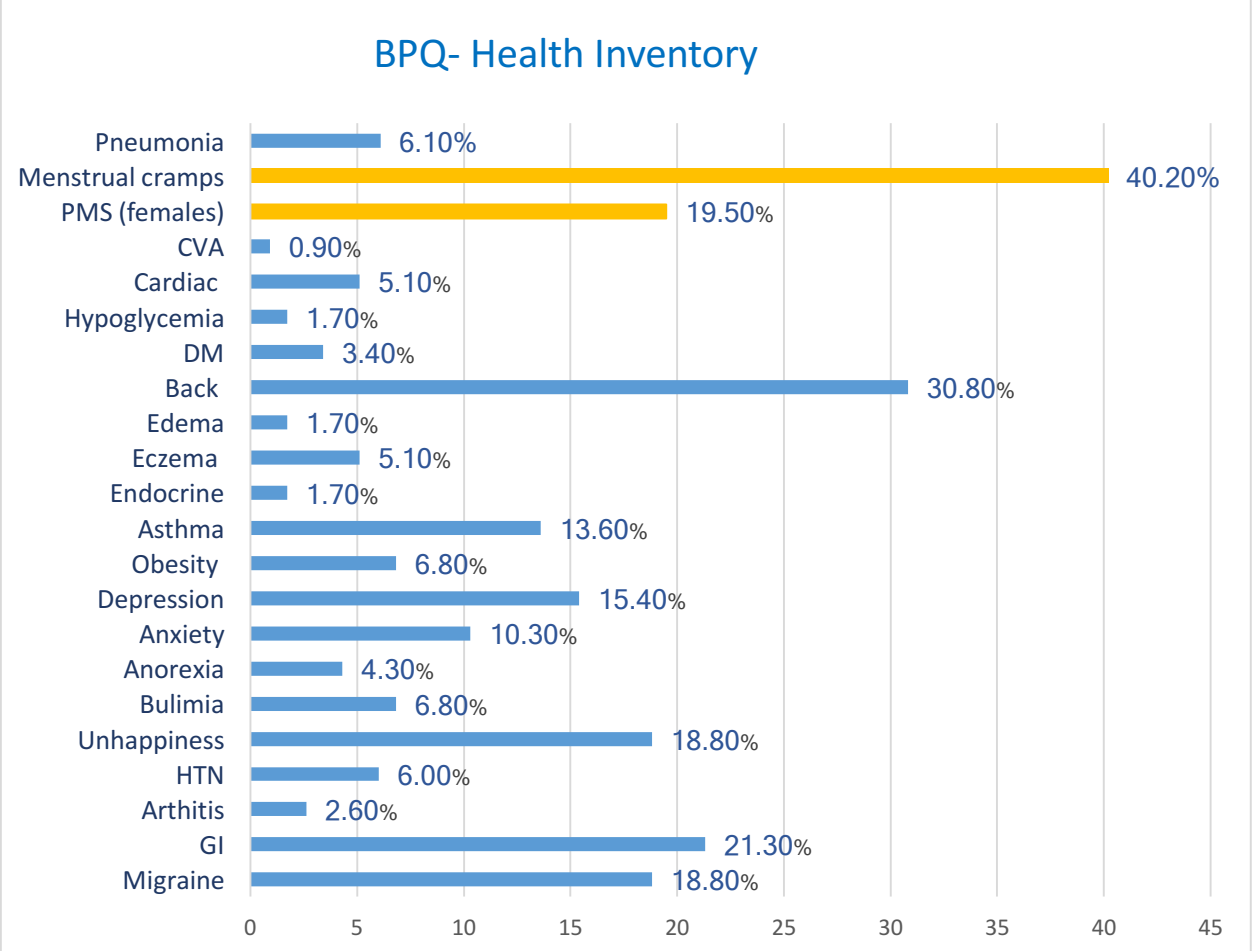
In this sample, 33.3% of the subjects met criteria for JHS (score ≥3/7 SQCH) with a significantly higher proportion of females in this group (p<0.001). Based on JHS scores, participants were classified into the JHS and the non JHS groups and different socio-demographic and BPQ variables were compared between these two groups. The JHS group reported significantly more visits to the psychiatrist (p=0.019) and scored significantly higher in the Body awareness (p=0.012), stress response (p=0.002), ANS reactivity (p=0.01), and in the health history inventory (p =<0.001) compared to the non-JHS group, see full results in table 8.

*Table 8. Study 4; Group differences in socio-demographic information and BPQ scores (*significant)*

Variable	TOTAL (n=117)	JHS (n=39)	Non-JHS (n=78)	Statistical test	*p*-value
Psych visits No Psych visits	32 (27.35%) 85 (72.65%)	16 (41%) 23 (59%)	16 (21%) 62 (79%)	χ^2=5.51	0.019*
Females Males	84 (71.8%) 33 (29.2%)	36 (92.3%) 3 (7.7%)	48 (61.5%) 30 (38.5%)	χ^2=12.15	< 0.001*
BPQ- Awareness	2.15±0.50	2.31 ±0.54	2.07±0.41	*t* = 2.56	0.012*
BPQ- Stress Response	2.21±0.80	2.55 ±0.99	2.05±0.65	*t* = 3.81	0.002*
BPQ- ANS reactivity	1.6±0.52	1.77±0.58	1.51±0.45	*t* = 2.61	0.010*
BPQ-Stress 1	2.86±0.69	2.91±0.67	2.83±0.70	*t* = 0.63	0.534
BPQ- Stress 2	1.83±1.42	1.88±0.88	1.80±1.62	*t* = 0.31	0.756
BPQ- Health history Inventory	6.45±6.37	9.54±6.56	4.88±5.69	*t* = 3.82	< 0.001*

The Health history inventory included some autonomic-related illnesses and the frequencies of each category are shown in Figure 7. The most frequent medical complaints among this nonclinical sample were back problems (30.8%), gastrointestinal problems (21.3%), migraines (18.8%), unhappiness (18.5%), and premenstrual syndrome (19.5%) and menstrual cramps (40.2%).

Figure 7. This figure shows the frequency of each autonomic-related illness measured by the health history in the whole sample



The frequencies of each variable of the health history inventory were compared between groups and the JHS subjects had significantly higher percentages of anxiety, depression, unhappiness, bulimia, anorexia, severe menstrual cramps, and eczema as shown in table 9. Non-significant results were not included in the table.

*Table 9. Study 4; Group differences in the health history inventory subscale (*significant).*

Health history Inventory	TOTAL	% JHS	% Non JHS	χ^2	*p*-value
Anxiety	10.3%	83.3%	16.7%	15.04	<0.001*
Depression	15.4%	77.8%	22.2%	18.9	<0.001*
Unhappiness	18.8%	72.7%	27.3%	18.9	<0.001*
Bulimia	6.8%	75%	25%	6.71	0.012*
Anorexia	4.3%	80%	29%	5.12	0.023*
Severe menstrual cramps	40.2%	51.2%	48.8%	5.72	0.016*
Eczema	7.7%	77.8%	22.2%	8.6	0.003*

6 DISCUSSION

6.1 STUDY 1 & 2: PSYCHIATRIC AND PSYCHOLOGICAL ASPECTS IN THE EHLERS-DANLOS SYNDROMES & JOINT HYPERMOBILITY, ANXIETY AND PSYCHOSOMATICS: TWO AND A HALF DECADES OF PROGRESS TOWARD A NEW PHENOTYPE.

Futures lines of research

First, a comprehensive model of illness is needed; the single "medical specialty" approach has to change for a multidisciplinary one. Models including both somatic and also psychiatric/psychological characteristics are required. A first approach was made through the ALPIM spectrum proposal, which is the acronym for anxiety and the domains of its most commonly occurring comorbidities: JHS/hEDS, pain disorders, immune disorders, and mood disorders [106]. The authors of this study hypothesized that the ALPIM syndrome have predictable psychiatric and medical comorbidities and found that significant associations between joint hypermobility and bipolar III, headache with bipolar II, and bipolar II with chronic fatigue syndrome. As discussed above, our group recently described the "Neuroconnective phenotype" which is a more comprehensive model of illness that includes the neglected somatic dimensions which can guide for earlier diagnosis and more specific treatments. More clinical studies should be done to determine the perimeter and the trans-diagnostic value this phenotype, which probably will contribute to the modern criteria like the Research Domain Criteria (RDoC).

Second, research on the underlying mechanisms is necessary, particularly to unmask the obvious but still occult genetic links. The DUP 25 in the chromosome 15 found among subjects suffering from both anxiety and JHS/hEDS [52], could not be replicated but it might be worthwhile to further investigate the possible genetic link with new genetic techniques such as genome-wide studies.

Third, combined treatments tackling both somatic and psychological features should be developed and tested for better evidence based treatments. No proper drug trials have been done so far and there is evidence of the higher utilization of psychotropic medication and also

the higher rates of premature treatment discontinuation due to side effects. Taking into account that these patients have multiple bodily complaints, physical approaches should be further studied. Along the same lines, yoga, meditation, sophrology and mindfulness are potential ways to be explored in systematic studies, since a lot of patients with this phenotype take advantage of these techniques. Finally, the therapeutic value of taking oral collagen reminds unknown and should be further explored.

From an evolutionary perspective, there may be evidence of a similar phenotype (JHS/hEDS and anxiety-like behaviors) in mammals which is currently under study in dogs by our group. If replicated, this finding would prove that this phenotype has endured through natural selection throughout evolution and most importantly, would give important evolutionary bases of its advantages. In humans, this phenotype provides advantages for performing artists (ex. ballet dancers) and sportsmen and sportswomen, but this needs to be further studied.

Lastly, comprehensive models of care taking a multidisciplinary approach should be implemented. Several experiences, particularly in England, where there is the London Hypermobility Unit at the Hospital of St John and St Elizabeth, may be the prototypical model. Besides, these strategies may facilitate earlier diagnosis and preventive strategies particularly among children should be tested and implemented. This may help to guide for more specific treatments and to avoid undesirable outcomes in the adulthood.

6.2 STUDY 3: JOINT HYPERMOBILITY IS ALSO ASSOCIATED WITH ANXIETY DISORDERS IN THE ELDERLY POPULATION

AD are highly prevalent in later life and have substantial consequences to the individuals and also to the healthcare system but they are often underdiagnosed and untreated. Clinical experience has long suggested that anxiety disorders are heterogeneous syndromes that vary markedly between individuals with respect to their clinical presentations, responses, longitudinal course, and risks of recurrence [107]. JHS has been repeatedly associated with AD in clinical and nonclinical populations and it can be used as a physical marker for homogeneous type of anxiety disorders in children and adults. In this novel study, we assessed if JHS can be used as a physical marker for anxiety disorder in the elderly population. We used both dimensional and categorical instruments to capture sub-threshold anxiety symptoms along with measurements of fear, panic, psychopathology and somatic symptoms.

Literature shows that Joint Hypermobility tends to decrease with age, and studies that assessed the JH in elder adults used the articular criteria only [27] , which do not consider the loss of agility secondary to aging. In this study, we evaluated JHS, the multi-systemic condition with "The Hospital del Mar criteria", a more comprehensive scale that includes some extra-articular symptoms that compared to other sets of criteria, have better internal reliability and homogeneity [32] . Besides this, we modified the cutoff range (1 point lower) to consider the aged population, as the regular cutoff points are usually applied in younger populations only. This may explain the relative high prevalence of JHS found in this sample; however, as expected, it is higher in women than men, which is in line with prior studies.

Subjects with JHS scored higher in the dimensional measurements of anxiety and fears which is in line prior findings, reinforcing the hypothesis that people with JHS have higher anxiety and intensity of fears. Other studies in non-clinical populations showed that individuals with JHS/hEDS scored significantly higher in state/trait and social anxiety scales [108]. The meta-analysis done by Smith [41] revealed that people with JHS/hEDS experience significantly

greater perception and fear intensity and have higher probability of agoraphobia and panic disorders, which is consistent with our findings.

The multiple regression analysis showed that both JHS and fears were predictors of anxiety disorders, which is consistent with prior studies, but to date this is the first study, this in the elderly population evaluating these variables. While the correlation between these two variables is well supported by current literature, the evidence about management and treatment of these patients it is still scarce [109]. Future research should further study this correlation to guide for novel therapies for early prevention and treatment.

Diagnostically, significant differences were found between both groups (JHS and non JHS). The JHS group had significantly higher rates of anxiety and depressive disorders, but for this second diagnosis the differences were not significant when patients with depression and comorbid anxiety were excluded from the analysis. This highlights solid correlation between anxiety-JHS that constitutes a specific phenotype that is seen across some psychiatric disorders such as depression, eating disorders, neurodevelopmental disorders and substance abuse [109] . The past year prevalence of AD in this sample was 16.7% and Reynolds et al. [6] recently published a large epidemiological study showing that the past year prevalence of AD tends to decrease by age, being approximately 11.4% in the elderly population with important gender differences. There is a debate whether the prevalence rates of psychiatric disorders increase or decrease with aging, however, the results seem to vary depending on the study design. Small studies seem to find an increase of the psychopathology while large epidemiological studies found opposite results. In the study done by Reynolds, the analysis was stratified by 4 different older age groups, being the past year prevalence of AD 14.81% within the age range of 55-65 y/o which is similar to our findings. The small sample size and the relatively young-middle age-old participants our study could explain the minor differences.

Limitations

There are some methodological limitations of the study deserve to be commented. First, sample size was small may not fully represent the general population and the mean age of the sample was relatively low. Secondly, fears were measured using a self-reported questionnaire, which is intrinsically subjective, although this situation was identical for subjects with and without joint hypermobility. Lastly, in the recently published DSM-5, the diagnostic criteria for several anxiety disorders may have been modified and thus our study may not fully reflect current diagnostic classification.

6.3 STUDY 4: BODY PERCEPTION IN A SAMPLE OF NONCLINICAL YOUNGSTERS WITH JOINT HYPERMOBILITY

In this study, we evaluated JHS and body perception in a sample on nonclinical youngsters in order to define body perception profiles in JHS.

The literature shows that JHS is usually more prevalent in pediatric and young populations ranging from 3-30%. Several factors are known to influence the prevalence old JHS including age, gender and ethnicity [25]. In this sample, the prevalence of JHS was slightly higher (33%) which could be explained by the higher frequency of females. The sample was homogenous in terms of age and race but females, besides being overrepresented, were significantly more hypermobiles. This is in line with other studies that have estimated that JHS is more frequent among females (ratio 3:1) [110].

Subjects with JHS had significantly higher scores in most of the BPQ subscales including body awareness, stress response, reactivity of ANS, and the health history inventory. No significant differences were found in the stress style 1 and 2 subscales. The Body Perception Questionnaire was developed to specifically assess subjective experiences of the function and reactivity of target organs and structures that are innervated by the autonomic nervous system. As mentioned above, it is based on the Polyvagal Theory [111] [62] which has provided a framework to generate hypotheses regarding the functional organization of the neural pathways that underlie unconsciously-appraised bodily states and their reactivity. The autonomic nervous system has been proposed as one of the key underlying mechanism behind the association between JHS and anxiety. Augmented or disordered awareness of such bodily signals is a feature of multiple clinical disorders such as anxiety, panic attacks, and depression [112] [113] [114]. In JHS, Mallorqui-Bague [56] studied a small sample of healthy volunteers and found that interception sensitivity mediated the relationship between state anxiety and hypermobility.

Subjects with JHS reported significantly more visits to the mental health professionals and had also significantly higher rates of self-reported anxiety, depression, unhappiness, bulimia, anorexia, severe menstrual cramps, and eczema. Despite we did not assess the prevalence of any psychiatric illness in this sample; the self-reported results on the health history inventory of the participants are congruent with prior research. The anxiety-JHS profile has been proven to be stable across several areas of the psychopathology including depression, substance abuse, eating, and neuro-developmental disorders [115]. Therefore, it is not surprising to find that people with JHS seek more mental health help compared to people without JHS. In terms of eating disorders, subjects with JHS have higher frequency of eating disorders and Baeza-Velasco [82] proposed a model of eating disorders in JHS that hypothesized that both articular (i.e. temporomandibular joint dysfunction) and extra-articular features (i.e. gastrointestinal sensitivities, food allergies) play a role in developing and maintaining these eating patterns. The high incidence of food sensitivities among people with JHS is suggestive of histamine hyper-reactivity and several allergic related problems have been described in JHS such as eczema [116]. Gynecological aspects of JHS have been largely ignored in the past, but it is now accepted that women with JHS/EDS-HT commonly suffer from irregular menses, meno/metrorrhagias, and severe dysmenorrhea, also known as severe muscle cramps. Together, these findings strengthen the hypothesis that the JHS phenotype constitutes a multisystemic condition and thus a multidimensional approach should be granted in this type of patients.

Limitations

This study has limitations. First, the study was conducted with a small sample that was homogeneous in terms of race, years of education and age and thus, the results cannot be extrapolated to the entire population. Another limitation is that medical and psychiatric manifestations were based on self-reports instruments and no objective measures were applied to ensure proper validity of the diagnosis.

7 CONCLUSIONS

In summary, the well-established association between a collagen condition and anxiety has open new dimension to better understand psychopathological and somatic conditions. In this thesis, we aimed to further explore the relationship between anxiety and JHS/hEDS and also wanted to describe the psychopathology associated with the JHS/hEDS. The main conclusions of the thesis derived from the included studies are presented below.

1. There is increasing amount of evidence pointing towards a high prevalence of psychiatric conditions among individuals with hypermobile type of Ehlers-Danlos syndrome (JHS/hEDS). A literature review confirms a strong association between anxiety disorders and JHS/hEDS, and there is also limited but growing evidence that JHS/hEDS is also associated with depression, eating and neuro-developmental disorders as well as alcohol and tobacco misuse.

2. The underlying mechanisms behind this association include genetic risks, autonomic nervous system dysfunction, increased exteroceptive and interoceptive mechanisms and decreased proprioception. Subjects with JHS have an atypical body perception profile characterized by higher awareness, stress response, and ANS reactivity. They also report higher frequency of autonomic related illnesses including anxiety, depression, bulimia, anorexia, unhappiness, severe menstrual cramps (in females only) and eczema and are more likely to seek mental health help compared to controls.

3. These findings support the hypothesis that the autonomic nervous system and body perception may play a key role in the development of anxiety and somatic illnesses among subjects with JHS/hEDS. The documentation of shared common abnormalities in both the autonomic nervous system and the collagen structure may represent a diathesis not yet identified, but worthy to investigate by subsequent studies.

4. The JHS/hEDS is also associated with anxiety disorders in the elderly population and could be used as a marker for a homogenous type of anxiety disorders in these types of population. These results may be a step toward a better understanding of the association between joint hypermobility and anxiety disorders but further studies are required to further clarify this association.

5. A multidimensional approach like the "Neuroconnective phenotype" should be used and implemented when evaluating this illness to ensure proper assessment of all the psychopathological aspects. Future lines of research should further explore the biological basis of this association to facilitate the prevention and earlier diagnosis, as well as to expand the therapeutic dimension.

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9 ANNEX

ARTICLE

Psychiatric and Psychological Aspects in the Ehlers–Danlos Syndromes

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There is increasing amount of evidence pointing toward a high prevalence of psychiatric conditions among individuals with hypermobile type of Ehlers–Danlos syndrome (JHS/hEDS). A literature review confirms a strong association between anxiety disorders and JHSh/hEDS, and there is also limited but growing evidence that JHSh/hEDS is also associated with depression, eating, and neuro-developmental disorders as well as alcohol and tobacco misuse. The underlying mechanisms behind this association include genetic risks, autonomic nervous system dysfunction, increased exteroceptive and interoceptive mechanisms and decreased proprioception. Recent neuroimaging studies have also shown an increase response in emotion processing brain areas which could explain the high affective reactivity seen in JHS/hEDS. Management of these patients should include psychiatric and psychological approaches, not only to relieve the clinical conditions but also to improve abilities to cope through proper drug treatment, psychotherapy, and psychological rehabilitation adequately coupled with modern physiotherapy. A multidimensional approach to this "neuroconnective phenotype" should be implemented to ensure proper assessment and to guide for more specific treatments. Future lines of research should further explore the full dimension of the psychopathology associated with JHS/hEDS to define the nature of the relationship. © 2017 Wiley Periodicals, Inc.

KEY WORDS: joint hypermobility; anxiety; psychopathology; neuroconnective phenotype; hypermobile Ehlers–Danlos syndrome

Professor Antonio Bulbena, M.D., M.Sc, Ph.D., is the Chair of the Department of Psychiatry at the Autonoma University of Barcelona with clinical, academic, and administrative contributions particularly in the area of psychosomatic medicine and anxiety disorders, dementia, chocolate and carbohydrates, clinical measurement in psychiatry, phobias, seasonality, and biometeorology. Has recently developed the Neuroconnective Phenotype and has published numerous books, book chapters, and scientific articles in peer-reviewed journals.

Carolina Baeza-Velasco, Ph.D., is a clinical psychology at the Paris Descartes University, with important contributions in the area of psychological assessment and treatment of patients with comorbid anxiety disorders and joint hypermobility among other conditions. Has published several articles about the psychological factors of EDS and related conditions.

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INTRODUCTION

The relationship between the JHS/hEDS and anxiety was an unexpected finding that we first described in 1988 at the Hospital del Mar in Barcelona [Bulbena et al., 1988]. It really was a clinical observation rather than a pathophysiological reasoning and the reiterated coincidence of the two conditions prompted us to study this association in more detail. Prior to this study, there were some scattered observations in the literature pointing to this new direction. In 1957, rheumatologist Rotés-Querol and Argany [1957] observed a remarkable degree of nervous tension suffered by patients with hypermobility. To a certain extent, there were some indirect references about the relationship between "visceroptosis" and anxiety/phobias in the classical psychosomatic literature [Flanders Dunbar, 1955].

Literature uses indistinctly Joint Laxity (the original name), Joint Hypermobility (the given name) and Elher–Danlos Syndrome-Hypermobile type (hEDS). Joint hypermobility (JH) is characterized by an extended range of motion of the joints, increased distensibility of joints in passive movements and hypermobility in active movement in the absence of another rheumatologic disease. JHS/hEDS is multisystem condition associated with musculoskeletal dysfunctions, possibly resulting from a glycoprotein deficiency and genetic alterations affecting the formation of collagen, which would explain tissue looseness, prolapsed organs, visceroptoses, pneumotorax, and vulnerability to trauma in these patients.

There are several sets of criteria that show minimal variations from the originally proposed by Rotés, although new self-assessment questionnaires have been added to the assessment methods of JHS [Hakim and Grahame, 2003; Bulbena et al., 2014]. A review paper of all the available criteria showed a high degree of agreement among all of them [Bulbena et al., 1992] but a more comprehensive set of 10 criteria obtained by cluster analysis was also proposed. However, the most often used are the "Beighton criteria" converted to a 9-point clinical scale by which subjects with a score ≥ 4 are considered as having JHS. In 2000, Grahame et al. [2000] developed the Brighton criteria to replace the Beighton criteria for the joint hypermobility syndrome (JHS). According to these criteria, the syndrome diagnosis is made taking into account the Beighton score and also some other clinical manifestations associated with hypermobility. The clinical assessment of the JHS/hEDS is not difficult but examiners should be trained in order to ensure the reliability of the exam.

Joint hypermobility (JH) is characterized by an extended range of motion of the joints, increased distensibility of joints in passive movements and hypermobility in active movement in the absence of another rheumatologic disease.

In this article, we review the psychopathology associated with JHS/hEDS, as well as the possible explanations for such association, the controversies, management, and future lines of research.

METHODS

The working group was composed of well-respected international clinician-researchers in the area of psychopathology with special interests in Ehlers–Danlos syndromes as part of the International Consortium on the Ehlers–Danlos Syndromes. Literature searches were conducted using the main electronic databases including the Cochrane Library, Informit, PsycINFO, PubMed, and Scopus. The main search terms used were "joint hypermobility syndrome," "joint hyperlaxity," "anxiety," and each separate psychiatric diagnostic category. Studies were included if they were published until September 2016, either in English or Spanish, if they reported any psychiatric conditions associated with joint hypermobility. The consensus was obtained after all authors completed their contributions and reviewed the manuscript on three separate occasions to ensure general agreement by all the authors. A total of 66 articles were included in the review.

LITERATURE REVIEW

Psychopathology

Herein, the syndromes joint hypermobility syndrome (JHS) and the hypermobile type of Ehlers–Danlos are considered as single entity (JHS/hEDS) for the purposes of this discussion defined by the previous diagnostic criteria, Brighton and Villefranche, respectively, except where the distinction is considered pertinent. See "The 2017 International Classification of the Ehlers-Danlos Syndromes" by Malfait et al., this issue.

Anxiety disorders

The relationship between JHS/hEDS and anxiety disorders has been widely explored during the past 30 years and current literature supports a solid association between these two variables [Bulbena et al., 2015]. Bulbena et al. [1993] conducted the first empirical case-control study where a sample of rheumatologic outpatients with JHS/hEDS were assessed and ~70% of hypermobile patients had some type of anxiety disorder, as compared to 22% in the controls [Bulbena et al., 1988]. A second study [Martin-Santos et al., 1998] evaluated outpatients with new

diagnoses of panic disorder and/or agoraphobia and found that JHS/hEDS was present in ~70% of patients with anxiety disorders compared to 10% in the controls. Garcia Campayo et al. [2010] also found a high prevalence of JHS/hEDS (61.8%) among subjects suffering from panic disorders compared with 10.9% among healthy controls.

Bulbena et al. conducted the first empirical case-control study where a sample of rheumatologic outpatients with JHS/hEDS were assessed and ~70% of hypermobile patients had some type of anxiety disorder, as compared to 22% in the controls.

Other studies in non-clinical populations showed that individuals with JHS/hEDS scored significantly higher in state/trait and social anxiety scales [Bulbena et al., 2004; Baeza-Velasco et al., 2011a]. A recent meta-analysis [Smith et al., 2014] revealed that people with JHS/hEDS experience significantly greater perception and fear intensity and have higher probability of agoraphobia and panic disorders. These authors pointed out that current evidence is derived from Mediterranean adult populations and highlighted that more research should be done to study this association in other populations.

The only incidence study that evaluated the relationship between JHS/hEDS and anxiety disorders was done in the general population with a 15 years follow-up [Bulbena et al., 2011]. Cumulative incidence of panic/agoraphobia disorder was significantly higher in the JHS/hEDS group (41.4%) with a relative risk of 22.3 (95% confidence interval [CI] 4.6–108.7, $P < 0.0001$). Incidence of social and simple phobia was also significantly higher in the JHS/hEDS group and anxiolytic drug use was nearly fourfold higher among JHS/hEDS group.

Mood disorders

Some studies examined the relationship between mood disorders and JHS/hEDS but the research on this area is significantly smaller compared to anxiety disorders. Two studies [Bair et al., 2003; Gurer et al., 2010] explored depressive disorders in JHS/hEDS subjects but no differences were found when comorbid anxiety was controlled for. In contrast, Pasquini et al. [2014] observed a higher rate of depressive symptoms in JHS/hEDS patients compared to controls. Other studies also revealed higher depressive symptoms in individuals with joint hypermobility (JH) without a known diagnosis of JHS/hEDS [Baeza-Velasco et al., 2011b; Murray et al., 2013]. The meta-analysis of Smith et al. [2014] concluded that people with JHS/hEDS commonly exhibit more anxiety and depressive symptoms. Hershenfeld et al. [2016] found 42.5% prevalence of psychiatric disorders (especially depression and anxiety) in a retrospective sample of JHS/hEDS subjects. Therefore, some preliminary evidence suggests higher rates of depressive symptoms among JHS/hEDS, especially when comorbid anxiety is present.

Personality disorders

The evidence in the field of personality disorder is very scarce and to date there is only one study published about it. Pasquini et al. [2014] observed that subjects with JHS/hEDS have a 5.8 relative risk of having a personality disorder, particularly anxious obsessive-compulsive personality disorder. Although this is in line with prior research studies that support a strong relationship between anxiety and JHS/hEDS, these results should interpreted with caution due to the lack of large, well-designed studies in this field.

Addictions

Most of the research about addiction in JHS/hEDS focused on substances (alcohol and tobacco mainly) and there are no studies about other dimensions of addiction such as behavioral addiction. Carlsson and Rundgren [1980] found significantly higher joint hypermobility scores among female alcoholic patients but did not diagnose hEDS in these same patients so the relevance is unclear. Interestingly, they proposed a link to hormonal dysregulation in chronic alcoholics to the increase in joint laxity. Lumley et al. [1994] reported that in a sample of EDS patients ($N = 48$; including adults and children and multiple types), 12% were found to have a history of alcohol or illicit drug use although the type of illicit substance was not specified. Since chronic pain was one of the major psychological stressors in that study, it would be interesting to know if there was a misuse of pain medications as well. Regarding tobacco addiction, Carbone et al. [2000] studied the bone density in JHS/hEDS and found that the control group smoked more tobacco and were taller compared to the JHS/hEDS group, which is not consistent with other findings that showed that patients with hEDS have a tendency towards the ectomorphic (thin and tall) phenotype and also that people with hEDS smoke more cigarettes. A longitudinal study found smokers had significantly higher JH scores [Baeza-Velasco et al., 2015a] which was consistent with prior studies. Coping with distress is frequently cited as a motive for the higher tobacco and alcohol use as both substances are known to reduce anxiety.

Eating disorders

Most studies seem to point toward a relationship between ectomorph somatotype (linear, thin, and usually tall) and JHS/hEDS [Bulbena et al., 2015], with higher rates of restrictive or compensatory eating disorders such as anorexia or bulimia. Some case reports described a co-occurrence of EDS and eating disorders such as anorexia nervosa (AN) [Al-Mufty and Bevan, 1977; Miles et al., 2007], although the type of EDS was not specified in the reports. Goh et al. [2013] hypothesized that since there is symptom overlap seen AN and JH such as gastrointestinal symptoms, orthostatic intolerance, and fatigue associated syndromes, JH is a possible

indicator of a familial disorder of connective tissue elasticity which potentially plays a causal role in the development of the eating disorder.

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Recently, Baeza-Velasco et al. [2015b] proposed a model of eating disorders in JHS/hEDS that provided some light about this phenomenon. The authors hypothesized that both articular and extra-articular features play a role in developing and maintain these eating patterns (Fig. 1).

Psychosis

There are some articles addressing the relationship between JHS/hEDS and schizophrenia. Bulbena et al. [2005] studied 124 patients with schizophrenia with and without comorbid JHS/hEDS and found JHS/hEDS was markedly more frequent within the schizophrenic-panic/phobic cluster (62.1%) [OR: 9.35, CI: 3.85–22.73, $P < 0.0001$]. Similarly, Bulbena et al. [2007] found that individuals with comorbid schizophrenia JHS/hEDS had higher rates of phobia/panic anxiety and more positive symptoms as well, and postulated that JH could be a clinical marker for this phenotype in schizophrenia. In a third case control study (schizophrenic patients vs. healthy controls) done by the same group evaluating the somatotype in schizophrenia, JHS/hEDS had comparable rates between the groups but there was a tendency toward positive association between anxiety-joint hypermobility and anxiety-ectomorphism [Pailhez et al., 2009]. A case report by Sienaert et al. [2003] described a case where a patient with comorbid schizoaffective disorder and classical EDS received electroconvulsive therapy, although it is unclear if the patient met diagnostic criteria for classical EDS.

Neurodevelopmental disorders

This is a burgeoning area of research that has developed over the recent years which seems to indicate a degree of co-occurrence of JHS/hEDS and some neuro-developmental disorders including attention-deficit/hyperactivity disorders (ADHD), developmental coordination disorder (DCD), and autism spectrum disorder (ASD).

In the area of ADHD, Eccles et al. [2014] found that adults with ADHD had higher rates of JH and symptoms of autonomic dysfunction compared to healthy controls. Another study, done by Harris [1998] that was published as a letter to the editor, found that the great majority (99%) of children with ADHD in his sample had JH, although this results should be interpreted with caution as it is based on clinical observations with no methodology reported. Similarly, Hollertz [2012]

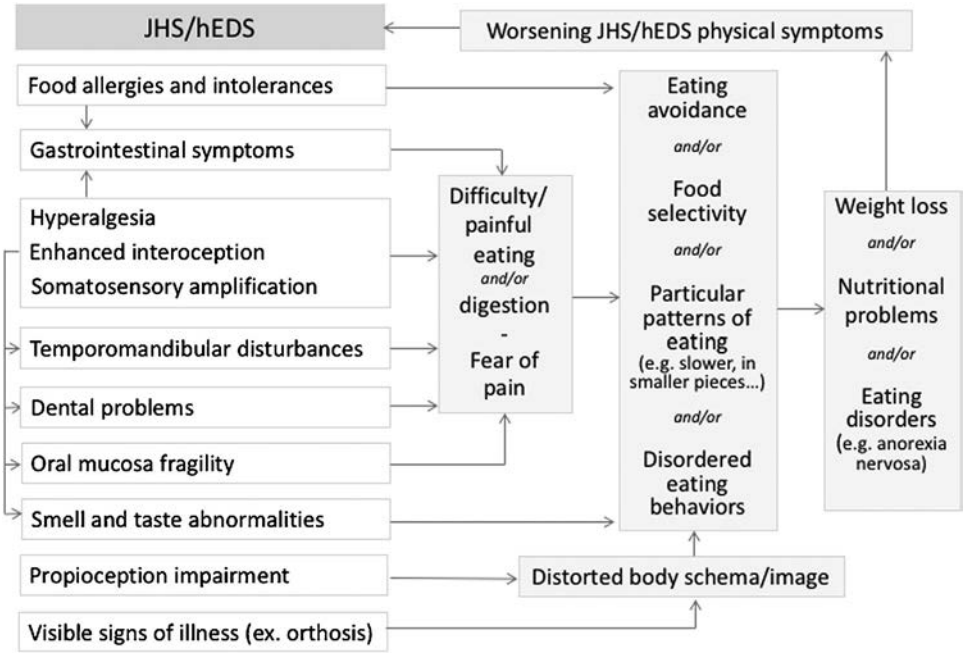

Figure 1. This figure reflects different extra-articular features such as gastrointestinal problems, temporomandibular disorders, and food intolerances that contribute to developing and maintaining disturbed eating behaviours and significant weight loss seen JHS/hEDS patients. See "Hypermobile Elhers-Danlos Syndrome (a.k.a. Ehlers-Danlos Syndrome type III and Ehlers-Danlos Syndrome Hypermobility Type): Clinical Description, and Natural History" by Tinkle et al., in this issue.

reported high co-occurrence of EDS and ADHD based on an observational study. Other authors such as Dogan et al. [2011] and Shiari et al. [2013] did matched case control studies and found that JH was significantly higher in the ADHD group as well as anxiety compared to healthy controls.

Concerning DCD, Kirby and Davies [2007] reported that children with DCD have more symptoms associated with JHS/hEDS including joint hypermobility, pain, and autonomic dysfunction compared to asymptomatic typically developing children. Jelsma et al. [2013] found a significantly higher mean score of JH in the DCD-group as compared to age-matched, typically developing children. Ghibellini et al. [2015] suggested that the relationship between JH and DCD may be due to poor proprioception in hypermobile children.

No articles are published regarding the relationship between ASD and JHS/hEDS but a few have looked at the prevalence of JH in ASD. Shetreat-Klein et al. [2014] did a matched case control study and found that ASD children have greater mobility of joints and more gait abnormalities compared to healthy controls. However, this study had a relatively small sample and excluded children with overt neurological problems, which may not be an accurate representation of the ASD population. Also, few case reports also highlighted the comorbidity ASD–JH [Tantam et al., 1990; Sieg, 1992; Takei et al., 2011], but further studies need to further explore the possible association of JHS/hEDS and ASD.

Psychiatric and Psychological Treatment for hEDS

Although no specific studies about psychopharmacologic treatment for hEDS have been published yet, there is significant evidence that JHS/hEDS patients take more anxiolytics than the counterpart. The overall use of psychotropic drugs was 41.4% in JHS/hEDS subjects compared to 13.9% in controls (OR: 4.38 CI 95% 1.8–10.9) [Bulbena et al., 2011].

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High levels of anxiety and depression are frequent in JHS/hEDS [Smith et al., 2014; Bulbena et al., 2015] and it has been shown that negative emotions may increase the experience of pain [Linton and Shaw, 2011]. Celletti et al. [2013] observed that patients with a JHS/hEDS had high scores of kinesiophobia. JHS/hEDS patients also have hyperalgesia [Castori, 2013], enhanced interoception [Mallorqui-Bague et al., 2014; Bulbena et al., 2015], and a tendency toward a somatosensory amplification [Baeza-Velasco et al., 2011b]. These aspects related to increased perception and/or reduced tolerance of pain [Feuerstein and Beattie, 1995; Pollatos et al., 2012], might influence the pain experience.

Dysfunctional coping strategies were also associated with JH [Baeza-Velasco et al., 2015a]. However, there are no studies exploring the coping strategies in JHS/hEDS and psychological aspects of pain perception merits more research to develop treatments programs. Some pilot cognitive behavioral therapy (CBT) experiences have been developed and suggested that CBT is valuable in the pain management of JHS/hEDS patients [Bathen et al., 2013].

Possible etiologies

Although it is possible that some psychiatric symptoms, risk or defensive behaviors, and personality traits can be a consequence of adaptation and difficulties in dealing with chronic illnesses, biological hypotheses have been considered to explain this association [Baeza-Velasco et al., 2015a]. The genetic link between anxiety and hyperlaxity should be further explored. In this sense, Gratacos et al. [2001] reported a cytogenetic anomaly (DUP-25) common to these two phenomena, although to date this study has not been replicated [Tabiner et al., 2003; Henrichsen et al., 2004]. Eccles et al. [2012] observed structural differences in areas of the brain implicated in emotion regulation in JHS.

Moreover, dysautonomia presents with symptoms that overlap with anxiety disorders. The perception/interpretation of physiological excitation play a role in anxiety disorders [Clark, 1986; Damasio, 1996; Craig, 2003] and JHS/hEDS patients have more intense interoception [Mallorqui-Bague et al., 2014] and are more likely to experience somatosensory amplification [Baeza-Velasco et al., 2011b]. Using multiple regression analysis, both JHS/hEDS and anxiety disorders were independently related to body perception and somatosensory amplification.

The Polyvagal Theory, proposed by Porges [2012], suggests that the evolution of the mammalian autonomic nervous system provides the neurophysiological substrates for adaptive behavioral strategies in both safe and dangerous environments. The theory provides a model to investigate the circuits that may be involved in dysautonomia and how atypical neural regulation of the autonomic nervous system that may function as a neural platform for several of the features observed in JHS/hEDS. Based on the Polyvagal theory [Porges and Furman, 2011], the Body Perception Questionnaire [Porges, 1993] has been applied to objectively quantify subjective reports of bodily reactions and states. The questionnaire identified atypical profiles in JHS/hEDS [Bulbena et al., 2014] and is being validated for clinical use.

In another study, trait anxiety scores did significantly correlate with both state anxiety and hypermobility

scores. Hypermobility scores were also associated with other key affective processing areas in the whole brain analysis [Mallorqui-Bague et al., 2014, 2015, 2016]. These findings increase our understanding of emotion processing in JHS/hEDS people and the mechanisms through which vulnerability to anxiety and somatic symptoms arises in this population.

Another physiological fact that may underlie this relationship is the strong value of the visceral afferent signals to the brain. This has been extensively studied by Critchley et al. [2013] who showed how different visceral inputs can influence thoughts, feelings, and behavior.

Considering the growing evidence of enhanced body awareness among JHS/hEDS along with the increased interception and somatosensory amplification, there might be an excess of alarming information which leads to psychological discomfort and psychiatric conditions.

Controversies

There are some controversies regarding the psychopathology associated with JHS/hEDS that should be addressed. First, patients with chronic pain and decreased functionality often display anxiety and depression [Bair et al., 2003], independently of the hEDS diagnosis. Another point is that hEDS is associated with multiple conditions like dysautonomia, which can cause a broad spectrum of physical complaints that can mimic anxiety-like symptoms. For instance, patients with dysautonomia experiencing intense heart rate fluctuations could be misdiagnosed with panic attacks. Another example could be the extreme fatigue caused by poor sleep architecture seen in these patients, that could be mistaken as depression. The key lies in being able to identify the cause of the anxiety and depression—if it is centrally mediated as a behavioral disorder or if it is the manifestation of associated conditions.

Another controversy in hEDS lies in diagnosing children or their parents with Conversion Disorder or Munchausen by Proxy respectively. These children often present with chronic pain, easy bruising, multiple joint dislocations, abdominal pain, dizziness, and fatigue that can be misdiagnosed as Conversion Disorder or Munchausen by Proxy. Barnum [2014] recently published a case of a child who had EDS but was misdiagnosed with conversion disorder and highlighted the stigmatizing consequences of making the wrong diagnosis in this population.

It is crucial that the physicians making the psychological assessment of hEDS patients are appropriately trained with the articular and extra-articular symptoms.

Management

The psychiatric and psychosocial issues have to be explored and properly evaluated in these patients. Pain, negative feelings, and poor emotion regulation are frequently associated with this condition. The consideration of all these aspects can help develop adapted protocols of evidence based psychiatric treatment and psychosocial interventions such as CBT (Table I).

Future lines of research

First, a comprehensive model of illness is needed; the single "medical specialty"

TABLE I. Roles of the Mental Health Professionals in the Management of JHS/hEDS

Objective/problem	Professional/intervention
Psychopathology (anxiety/mood disorders), Associated mental disorders (e.g., Addictions, sleep disorders, etc.)	Psychiatrist (diagnostic and treatment issues) Clinical/health psychologist (CBT) (psychotherapy with or without pharmacotherapy)
Management of chronic pain and negative emotions	Clinical/health psychologist (cognitive-behavioral approach: CBT). Psychiatrist Psychiatric nurse Occupational therapist
Improve knowledge about disease	Therapeutic patient education (pluridisciplinary)
Improve/develop competences to manage chronic disease (e.g., self-efficacy, coping strategies, etc.)	Clinical/health psychologist (CBT). Psychiatric nurse Occupational therapist
Neurodevelopmental disorders in childhood	Child/developmental psychiatrist Child/developmental psychologist (CBT)
Cognitive impairments (attention, memory, etc.)	Neuropsychologist
Support	Clinical psychologist (supportive therapy, different approaches) Psychiatric nurses, OT

This table defines the different r*oles of the mental health professionals in the management of* JHS/hEDS. The objective or problematic areas are introduced in the left column and the proposed intervention in the right column.

approach has to change for a multidisciplinary one. Models including both somatic and also psychiatric/psychological characteristics are required. A first approach was made through the ALPIM spectrum proposal, which is the acronym for anxiety and the domains of its most commonly occurring comorbidities: JHS/hEDS, pain disorders, immune disorders, and mood disorders [Coplan et al., 2015]. The authors of this study hypothesized that the ALPIM syndrome have predictable psychiatric and medical comorbidities and found that significant associations between joint hypermobility and bipolar III, headache with bipolar II, and bipolar II with chronic fatigue syndrome.

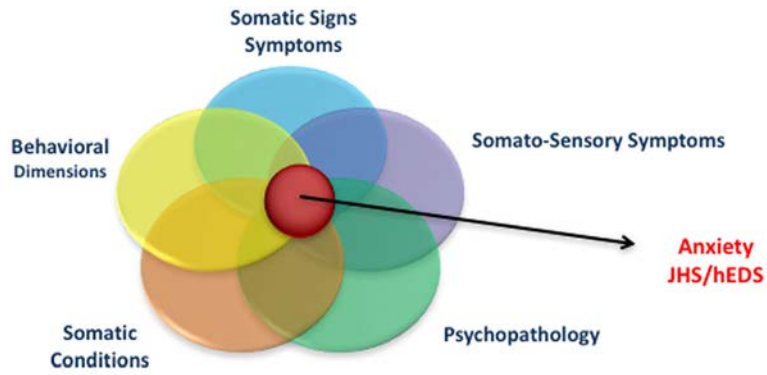
A more recent proposal is the "Neuroconnective phenotype" (Fig. 2), in which, around a common core Anxiety-hEDS, it includes five dimensions: behavioral, psychopathology, somatic symptoms, somatosensory symptoms, and somatic illnesses.

Second, research on the underlying mechanisms is necessary, particularly to unmask the obvious but still occult genetic links. The DUP 25 in the chromosome 15 found among subjects suffering from both anxiety and JHS/hEDS [Gratacos et al., 2001], could not be replicated but it might be worthwhile to further investigate the possible genetic link with new genetic techniques such as whole genomic analyses. The psychophysiological circuits involved between the core features of JHS/hEDS (namely pain and body awareness) and their psychiatric correlates need to be uncovered. These neural correlates may also provide clues to unveil the emotional dysregulation found in JHS/hEDS.

Third, combined treatments tackling both somatic and psychological features should be developed and tested for better evidence based treatments. When talking about phenotypes in psychiatry, authors tend to include only behavioral and psychopathological traits, which again, represents a bias against somatic or body characteristics. Such restrictive view prevents the development of more comprehensive treatments. However, anxiety cases with JHS/hEDS tend to show more somatic features and therefore, it would be worthwhile exploring and developing more specific treatments for them.

Fourth, comprehensive models of care taking a multidisciplinary approach should be implemented. Several experiences, particularly in England, where there is the London Hypermobility Unit at the Hospital of St. John and St. Elizabeth, may be the prototypical model.

Fifth, considering the evidence of the increased risk associated with JHS/hEDS to develop anxiety disorders, preventive strategies particularly among children should be tested and implemented. This may help to guide for more specific treatments and to avoid undesirable outcomes in the adulthood. However, while the link between



- Behavioral Dimensions are patterns of defensive mechanisms that are often identifiable at the extreme of a continuous axis (i.e fight/flight, restriction (avoidance)/dependency
- Somatic symptoms include dysautonomia, asthenic somatotype, "blue " sclera*, "easy bruising", eczemas*, dyskinesia, dislocations, prolapses and hypertrophic scars*
- Somatic Conditions: irritable bowel syndrome, dysfunctional esophagus, chemical sensitivities, dizziness, fatigue, fibromyalgia, -dynias, hypothyroidism, asthma, migraines, temporomandibular dysfunction and food intolerances.
- Psychopathology: increased interoception, exteroception, decreased proprioception, anticipatory anxiety, high loss sensitivity, and high positive confrontation.
- Somato-sensory symptoms include increased olfactory sensitivity, eye-contact difficulty, selective photophobia, dyspnea, dysphagia, choking, palpitations, joint pain and enhances sensitivity to weather and chemicals

* *These features have been previously described in the Neuroconnective phenotype*

Figure 2. The Neuroconnective phenotype. The Neuroconnective model is a proposal that may be useful for clinical practice disorders and of some psychosomatic conditions. It was described after the study and careful consideration of clinical and nonclinical data, pathophysiological mechanisms and the present anxiety nosological status. It is built around the core association of Anxiety-JHS/hEDS and it includes behavioral, psychopathology, somatic symptoms, somatosensory symptoms, and somatic illnesses dimensions. Each of the five dimensions includes features that may be present at different degrees and with individual variations and all dimensions incorporate patterns, clinical symptoms, signs and illnesses seen in these patients.

JHS/hEDS and anxiety disorders has been well established, there is limited evidence regarding the other dimensions of the JHS/hEDS psychopathology that should be further addressed in subsequent studies.

CONCLUDING REMARKS

To conclude, patients with JHS/hEDS often suffer from anxiety disorder and the link between these two variables has been repeatedly found in the literature. There is limited literature about other dimensions of the JHS/hEDS psychopathology that should be further addressed in subsequent studies.

In any case, a more careful psychiatric and psychological approach should be taken along other physical treatments to manage and treat this multisystem condition. A new model described as the Neuroconnective phenotype is proposed to evaluate the different dimensions of the pathology associated including behavioral patterns, clinical symptoms, and related illnesses

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Joint Hypermobility, Anxiety and Psychosomatics: Two and a Half Decades of Progress Toward a New Phenotype

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Abstract

The strong association between a heritable collagen condition and anxiety was an unexpected finding that we first described in 1988 at the Hospital del Mar in Barcelona. Since then, several clinical and nonclinical studies have been carried out. In this paper, after summarizing the concept and diagnosis of joint hypermobility (hyperlaxity), we review case-control studies in both directions (anxiety in joint hypermobility and joint hypermobility in anxiety disorders) as well as studies on nonclinical samples, review papers and one incidence study. The collected evidence tends to confirm the strength of the association described two and a half decades ago. The common mechanisms that are involved in this association include genetics, autonomic nervous system dysfunctions and interoceptive and exteroceptive processes. Considering clinical and nonclinical data, pathophysiological mechanisms and the presented nosological status, we suggest a new Neuroconnective phenotype, which around a common core Anxiety-Collagen hyperlaxity, includes five dimensions: behavioral, psychopathology, somatic symptoms, somatosensory symptoms, and somatic illnesses. It is envisaged that new descriptions of anxiety disorders and of some psychosomatic conditions will emerge and that different nosological approaches will be required. The Neuroconnective model is a proposal that is under study and may be useful for clinical practice.

History of Link Joint Laxity – Anxiety

The relationship between a heritable collagen condition and anxiety was an unexpected finding that we first described in 1988 at the Hospital del Mar in Barcelona [1]. It really was a clinical observation, rather than a pathophysiological reasoning.

While working at the psychiatric outpatient clinic, we repeatedly found a particular rubber stamp in the medical records of most of our patients suffering from anxiety: 'Hiperlaxitud

Articular'. That stamp was put there by the rheumatologist JC Duró, who was using it to systematically collect criteria for the Joint Hypermobility Syndrome (JHS) that had been described and studied by his mentor, Prof. Rotés. The reiterated coincidence of the two conditions, anxiety and the collagen condition, prompted us to study this association in more detail.

This observation prompted us to send a letter containing preliminary results to *The Lancet* [1], and soon after, we carried out the first case-control study.

Considering the high prevalence of mood disorders in patients suffering from collagenosis, psychiatrists have begun to associate collagen conditions with autoimmune illnesses, such as systemic lupus erythematosus or rheumatoid arthritis, whereas structural collagen disorders (mainly heritable) seemed to be less in mind due to the lack of knowledge of the psychiatric status of these patients.

However, scattered observations pointed in this new direction. In 1957, rheumatologist J. Rotés observed a remarkable degree of nervous tension suffered by patients with hypermobility [2]. To a certain extent, there were some indirect references about the relationship between 'visceroptosis' and anxiety/phobias in the classical psychosomatic literature [3]. On the other hand, in 1980, Carlsson and Rundgren [4] found higher hypermobility scores in alcoholic patients compared to controls. Although not mentioned, the case group might have consisted of a high percentage of patients with anxiety.

What is Joint Laxity (Hypermobility) Syndrome

In order to clarify the terminology throughout this paper, we shall indistinctly use joint laxity (the original name) and joint hypermobility (JH; the given name). Although the second is more often used in English publications, it in fact refers to a rather unspecific consequence (increased mobility), whereas hyperlaxity more correctly refers to the intrinsic mechanism (increased laxity of fibers).

The condition was described for the first time about 60 years ago, when it was properly identified and associated with pathology of the musculoskeletal system [2]. The original name proposed by Rotés was 'joint laxity' (Laxité Articulaire), and it was published in a French journal *(Revue du Rhumatisme)*. In 1964, Carter and Wilkinson, also using the term 'joint laxity', published a relevant paper in which they proposed diagnostic criteria [5]. In 1973, after an epidemiological study by Beighton et al. [6], who used both 'joint laxity' and 'joint mobility', the syndrome gained general interest in rheumatology and, by then, was renamed JH and began to be studied in a broader way as a separate entity [7]. Later on, the seminal work of Rodney Grahame was very important for the revisiting of JHS by rheumatologists. Grahame has published three editions of the Beighton book [8] as well as other books and has boosted clinical research on this topic [9, 10]. Another prominent author who has provided insightful clinical descriptions of JHS is Dr. J. Bravo [11].

JHS has an estimated prevalence in the general population of 10–20%. It is more frequent in females (3:1), and it is one of the connective tissue hereditary disorders that also include other conditions such as Ehlers-Danlos syndrome (EDS), Marfan syndrome and osteogenesis imperfecta [8]. In fact, it does overlap with EDS type III. JHS has an autosomal dominant pattern, and twin studies showed that genetics, rather than environmental factors such as training, accounts for at least 70% of the phenotype variance. Joint hypermobility is characterized by an extended range of motion of the joints, increased distensibility of joints in passive movements and hypermobility in active movement in the absence of another rheumatologic disease.

JHS is more common in childhood and tends to decline with age. The prevalence is higher in

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women, and there are probably ethnic differences, which suggests genetic variations. JHS is also associated with musculoskeletal dysfunctions, possibly resulting from a glycoprotein deficiency and genetic alterations affecting the formation of collagen, which would explain the tissue looseness, prolapsed organs, visceroptoses, pneumothorax and vulnerability to trauma in these patients.

Clinical features of JHS can be articular or extra-articular and are always related to the connective tissue. Arthralgia, lumbalgia, soft-tissue rheumatism (e.g., epicondylitis, tenosynovitis, and bursitis), recurrent dislocations, childhood scoliosis, or rheumatoid arthritis are some common articular features [11, 12]. On the other hand, hernias, varicose veins, 'easy bruising', hypertrophic scars and keloids, uterine or rectal prolapse, spontaneous pneumothorax, fibromyalgia, dysautonomia and other conditions linked to panic disorders (PDs) such as asthma, mitral valve prolapse (MVP), thyroid dysfunction or irritable bowel syndrome, are some of the best-known, extra-articular features of JHS [12, 13].

The Diagnosis of Joint Hypermobility (Hyperlaxity)

Several sets of criteria show minimal variations from the original disease proposed by Rotés, although new self-assessment questionnaires have been recently added to the assessment methods of JHS [14, 15]. A review paper of all available criteria showed a high degree of agreement among all of them [16], but a more comprehensive set of 10 criteria that were obtained by cluster analysis was also proposed. However, the most often used are the 'Beighton criteria', which is a nine-point clinical scale by which subjects with a score ≥4 are considered as having JH. The condition is characterized through the examination of five body areas, each one receiving a separate score of hyperextension: fifth fingers, thumbs, elbows, knees and trunk.

In 2010, Grahame [17] developed the Brighton criteria to replace the Beighton criteria for JHS. According to these criteria, the diagnosis of the syndrome is made by taking into account the Beighton score as well as some other clinical manifestations associated with hypermobility. As expected, the correlation between them is very high, but they are seldom used outside of rheumatology. The main sets of criteria are shown in table 1.

The clinical assessment of the Joint Laxity Syndrome is not difficult, but examiners should be trained in order to ensure the reliability of the exam. Our group has developed a 2-day training course that includes a support CD [18].

Clinical Studies

The first case-control study on the association between joint hypermobility and anxiety disorders was published in 1993 [19]. Patients were recruited from an outpatient rheumatology clinic, and the final study included 114 JHS cases and 59 controls. A high prevalence of anxiety disorders within the JH group (70%) was found compared to the control group (20%), with PD/agoraphobia (PD/A) (OR 4.12) and simple phobia (OR 3.03) showing the most significant correlations. MVP was only found in subjects with JH, and those patients were more likely (OR 2.95) to suffer from anxiety disorders compared to subjects without MVP; however, the association did not reach statistical significance.

Later, we carried out the reverse case-control study, that is to say, we blindly assessed joint hypermobility among anxiety patients compared to controls, who were carefully matched by age and gender, in a general teaching hospital [20]. The sample included 99 newly diagnosed patients with PD and/or agoraphobia and 163 controls who were recruited from the psychiatric (n = 99) and medical clinics (n = 64). The prevalence of JH was significantly higher (70%) in the PD/A group compared to the psychiatric (10%) and medical

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Table 1. Hypermobility criteria, description of Beighton, and Hospital del Mar and Brighton criteria, with suggested cut-off points

Beighton criteria

1. Passive dorsiflexion of the little fingers beyond 90° (one point for each hand).
2. Passive apposition of the thumbs to the flexor aspects of the forearm (one point for each thumb).
3. Hyperextension of the elbows beyond 10° (one point for each elbow).
4. Hyperextension of the knee beyond 10° (one point for each knee).
5. Forward flexion of the trunk with knees fully extended so that the palms of the hands rest flat on the floor (one point).

A general score of 4/5 in the Beighton system, which is the usual cut-off point in clinical practice, is proposed in order to diagnose a case.

Hospital del Mar Criteria

Upper extremities

1. Passive apposition of the thumb to the flexor aspect of the forearm at a distance of less than 21 mm.
2. The passive dorsiflexion of the fifth finger is 90° or more.
3. The active hyperextension of the elbow is 10° or more.
4. External rotation of the shoulder up to more than 85°.

Lower extremities; supine position

5. The passive hip abduction can be taken to an angle of 85° or more.
6. Hypermobility of the rotula.
7. Hypermobility of the ankle and foot.
8. Dorsal flexion of the toe of 90° or more.

Lower extremities; prone position

9. Hyperflexion of the knee.
10. Ecchymoses.

Bulbena et al. [16] propose to consider males with a score of 3/4 probable cases of joint hypermobility and women with a score of 4/5 probable cases of joint hypermobility. For age, it is suggested that patients older than 40 with a score of 3/4 probable cases of joint hypermobility and that patients younger than 40 years with a score of 4/5 probable cases of joint hypermobility be considered. A general score of 3/4 in the Hospital del Mar system, which is the usual cut-off point in clinical practice, is proposed.

Brighton Criteria

Major criteria

1. A Beighton score of 4/9 or more (either currently or historically).
2. *Arthralgia* for longer than 3 months in 4 or more joints.

Minor criteria

1. *Beighton* score of 1, 2 or 3 (0, 1, 2 or 3 *if aged 50 years or older*).
2. *Arthralgia* in 1–3 joints, *lumbalgia* for more than 3 months, spondylosis or spondylolysis/spondylolisthesis.
3. *Dislocation/subluxation* in more than one joint or in one joint on more than one occasion.
4. *Soft tissue rheumatism* in three or more lesions (e.g., epicondylitis, tenosynovitis, bursitis).
5. *Marfanoid Habitus* (tall, slim, span/height ratio >1.03, upper/lower segment ratio <0.89, arachnodactily).
6. *Abnormal skin:* striae, hyperextensibility, thin skin or papyraceous scarring.
7. *Eye signs*: drooping eyelids or antimongoloid slant.
8. *Varicose veins, hernia or uterine/rectal prolapse*.

BJHS is diagnosed if the patient presents 2 major criteria, 1 major and 2 minor criteria, or 4 minor criteria. Two minor criteria are enough when there is a first-degree relative who is clearly diagnosed with the syndrome. BJHS is excluded by the presence of Marfan or Ehlers-Danlos syndrome. The 1st major and 1st minor criteria exclude each other, as do the 2nd major and 2nd minor criteria.

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controls (12%). In this study, patients with PD/A were 17 times more likely to suffer from JH.

Lumley et al. [21] evaluated the psychosocial functioning of patients suffering from EDS (JHS is considered EDS type III). The patients were selected from an outpatient research clinic, and the results showed that the EDS type III group had higher anxiety, depression, and interpersonal sensitivity scores as well as higher scores for the symptomatology checklist and pain scales.

Other lines of research studied possible specific somatotype characteristics in patients with PD/A [22]. Patients with panic and/or agoraphobia from an outpatient mental health clinic were compared to psychiatric and medical controls matched by age and gender. Within the entire sample, the asthenic somatotype was associated with higher JH scores. Interestingly, the prevalence of an asthenic somatotype was at the same time significantly higher in the panic/agoraphobia group (33.3%) compared to the psychiatric (19.2%) and medical (18.7%) controls. The authors finally concluded that the relationship between PDs and asthenic somatotype might be mediated through JHS. These results were confirmed by another study carried out by the same group in 2014 [23]. This study included 60 patients with PD/A and 60 controls and found that an ectomorphic somatotype was independently related to JH status [OR 3.25, 95% CI 1.35–7.8, $p = 0.008$].

Nevertheless, some studies failed to find a significant correlation between PD and JH. The study by Benjamin et al. was carried out in Israel on 101 patients with PD and on 39 controls [24]. The authors also attempted to examine the possible association between reactivity to carbon dioxide and JH. The rate of JH did not differ between the cases and controls or between JH and carbon dioxide responses. However, they used the crude number of hyperlax joints instead of the scoring method, which carries the cut-off point to the extreme of the distribution and therefore is not fully comparable to other studies. On the other hand, the instruments used to assess anxiety in these patients (the self-rating scale of the National Institute of Mental Health, DSM IV panic symptoms scores and 100-mm visual analogue scales of anxiety) are uncommon and could explain the results of the study.

Gulpek et al. designed a study to test the association between JHS and PD and to determine whether MVP accounted for or changed this association [25]. The sample consisted of 115 subjects who were divided into 3 groups. The first group (n = 42) included patients with PD and MVP, the second group (n = 35) consisted of patients with PD without MVP, and the third group (n = 38) had patients with MVP and no psychiatric diagnosis. No significant differences were found in prevalence or severity of JH between the groups according to the Beighton criteria scoring. However, JH was present in 59.5% of PD patients with MVP and in 52.6% of the control subjects. Compared to other studies, the prevalence of JH in the control group was never found to be as high as in this study. Since the prevalence of JH was higher in patients with PD and MVP (59.5%), the authors suggested that MVP affects the prevalence of JH in PD. The prevalence of PD was also higher in the JH group compared to the controls.

Another research group from Turkey studied the relationship between thorax deformity, anxiety and joint hypermobility. Fifty-two males with thorax deformity and 40 healthy controls from a general outpatient medical clinic were selected to participate in the study [26]. Twenty patients (40%) from the cases group met criteria for JH, and those subjects had significantly higher anxiety scale scores, particularly for PD. All of the cases (with and without JH) had higher anxiety scores compared to the controls.

Ercolani and his team designed a study to assess the psychological features of the JHS [27]. They recruited 30 JH subjects and 2 control groups: 25 healthy subjects and 30 fibromyalgic patients. The JH group showed significant psychological distress and increased frequency and

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intensity of somatic symptoms compared to both control groups.

Garcia-Campayo designed a case-control study to assess the association between JHS, PD and fibromyalgia [28]. The sample included 220 patients and was divided into 4 different groups. The first group included newly diagnosed PD patients; the second group included patients with psychiatric diagnosis other than anxiety; the third group included patients with fibromyalgia; and the last group consisted of healthy controls. This study also confirmed the higher prevalence of JH in the PD group (61.8%) as well as an intermediate prevalence (25.4%) in fibromyalgia patients. There was a significant correlation between the Beighton criteria (JH) and panic anxiety scale scores.

One recent study provided insight into the importance of autonomic symptoms, such as the hypermobility type of EDS [29]. This group included 80 patients with EDS JH, as well as eleven patients with classical EDS, 7 with vascular EDS, 38 with fibromyalgia and 43 healthy controls. The total autonomic symptom burden was higher in EDS JH (57.9 ± 21.57) than in the other groups but was comparable to the fibromyalgia group (53.8 ± 19.85). They concluded that joint hypermobility and neuropathy might play a role in the development of autonomic symptoms.

In the same line of research, another study described the life experience of EDS JH patients and the impact of the symptoms on daily functioning [30]. The most frequent physical symptoms were joint pain (99%), hypermobility (99%) and limb pain (91%). They also reported a high frequency of other conditions such as chronic fatigue (82%), anxiety (73%), depression (69%) and fibromyalgia (42%). These studies are summarized in table 2.

Nonclinical Studies

Multiple nonclinical studies have assessed the relationship between these two variables in the general population. Our group recruited 1,305 subjects from the general population and found that patients suffering from JH were significantly more likely to suffer from PD (OR 8.19; 95% CI 3.41–19.67), agoraphobia (OR 5.89; 95% CI 2.98–11.66) and social phobia (OR 7.79; 95% CI 2.44–24.85) [31]. Concerning other anxiety conditions, no increased risk was found for simple phobia alone, obsessive-compulsive disorder alone, generalized anxiety disorder alone, dysthymic disorder alone or major depression alone when panic and agoraphobia were excluded. Therefore, the authors concluded that the features of JHS should be used as routine screening.

The same group recruited patients from the medical department of a large auditing and consulting firm of legal services in Barcelona and studied the possible relationship between anxiety and JH in this group of nonclinical subjects [32]. Males and females with JHS showed significantly higher trait anxiety scores (median scores 11, $p < 0.05$; and 17, $p < 0.001$, respectively) than nonhypermobile subjects; however, the difference in state anxiety was not significant for any gender. Both trait and state anxiety showed modest but significant correlations with JHS (Spearman's rho, 0.10–0.16; $p < 0.05$). This was the first article that showed higher anxiety levels in nonclinical subjects with JHS.

Some studies assessed the relationship between JH and fears. Our group designed a cross-sectional study to compare cultural fears in subjects with and without joint hypermobility [33]. The sample was recruited from a rural town, and JH was assessed using Beighton's criteria. The mean scores of the fear survey were higher in the JH group, and significant differences were found between groups, reinforcing the hypothesis that the intensity of fears is greater in subjects with JH. These results showed that the association between JH and phobic anxiety might represent a susceptibility factor for these anxiety conditions.

In the same line of research, another study was designed to see if the relationship between fears and JH was influenced by chocolate consumption

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Table 2. Characteristics of clinical and non-clinical studies on the association between joint hypermobility and anxiety

Study (author/ year/country)	Design	Setting	Sample	Variables studied	Main results
Clinical studies					
Bulbena* [1], 1988 [19], 1993 Spain	Case control	Rheumatology outpatient clinic	114 JH 59 controls	Anxiety: HAD-A EPQ, SCID III JH: Beighton	Significant association between JH and PD/A [OR 10.7 (4.8–23.8)] and simple phobia [OR 5.8 (2.0–16.20)]. No association with GAD [OR 2.5 (0.6–9.4)] JH patient with MVP, did not present with more anxiety
Martin-Santos* [20], 1998 Spain	Case control	Outpatient psychiatric and medical clinic	99 newly diagnosed PD/A 99 psychiatric controls 64 medical controls	Anxiety: HAM A/D, SCID III JH: Beighton Other: ECHO	JH found in 67.7% of patients with anxiety [OR 18.6 (8.6–40.5)] (10.1% in psychiatric control and 12.5% in medical control).
Lumley [21], 1994 USA	Case control	Outpatient research clinic	21 EDS III/JH 20 controls (other EDS)	Anxiety: HAM-A JH: EDS subtypes	EDS III (JH) higher scores for anxiety, depression and interpersonal sensitivity and greater scores for symptomatology and pain
Bulbena* [22], 1996 Spain	Case control	Outpatient mental/ medical clinic	99 PD/A 99 psychiatric controls 64 medical controls	Anxiety JH: Beighton Other: *Quetelet index*	Significant correlation between asthenic somatotype and PD/A [OR 2.23] PD/A and asthenic somatotype may be medication through JH
Pailhez* [23], 2014 Spain	Case control	Outpatient clinic	60 PD/A 60 controls	Anxiety: JH: Other: somatotype, sociodemographic	Ectomorphic somatotype was independently related to JH status [OR = 3.25, 95% CI 1.35–7.8, p = 0.008]
Benjamin [24], 2001 Israel	Case control	Anxiety out-patient clinic	101 PD/A 30 healthy controls	Anxiety: NIMH, PSS, VAS 100 mm JH: Beighton	JH = in both groups No association between carbon dioxide response and JH
Gulpek [25], 2004 Turkey	Case control	Outpatient psychiatric clinic	36 PD/A 42 PD/A + MVP 38 MVP	Anxiety: SCID IV JH: Beighton Other: ECHO	JH = 3 groups PD/A higher JH MVP may affect JH prevalence in PD
Gulsum [26], 2007 Turkey	Case control	Outpatient clinic	52 thorax deformity 40 controls	Anxiety: SCID, HAM-A JH: Beighton Other: thorax diameter	21 patients with TD had JH + (40%) JH group had higher anxiety scores (especially PD). TD group had higher anxiety scores (JH + and –)
Ercolani [27], 2008 Italy	Case control	General outpatient medical clinic	JH 30 30 control fibromyalgia 25 healthy control	Anxiety: DSM IV JH: Beighton Others: SCL-90-R, IBQ, SQ, FSF	JH group showed psychological distress and increased frequency and intensity of somatic symptoms
Garcia-Campayo [28], 2010 Spain	Case control	Primary care clinic	55 PD/A 55 psychiatric controls 55 fibromyalgia controls 55 healthy control	Anxiety: PAS, STAI JH: Beighton Other: SPPI	Prevalence of JH in PD was higher than in controls Prevalence of JH in PD was 61.8% Significant correlation between PAS scores and Beighton criteria
De Wandele [29], 2014 Belgium	Case control	Outpatient clinic	80 EDS-JH 11 classic EDS 7 vascular EDS 38 fibromyalgia 43 controls	Anxiety: HADS JH: GHQ Others: ASP, QOL, SF 36, GHQ, fatigue checklist, Baecke physical activity	The total autonomic symptom burden was higher in EDS-HT (57.9 ± 21.57) than in the other groups but was comparable to FM (53.8 ± 19.85)

Table 2. Continued

Study (author/ year/country)	Design	Setting	Sample	Variables studied	Main results
Murray [30], 2013 USA	Cross-sectional	Outpatient clinic	466 adults with EDS JH	237 online survey	High frequency of chronic fatigue (82%), anxiety (73%), depression (69%), and fibromyalgia (42%) among EDS JH
Nonclinical studies					
Bulbena* [31], 2004 Spain	Cross-sectional	General population	1,305 subjects	Anxiety: JH: Beighton MVP	Significant association between JH and PD/A [OR 10.7 (4.8–23.8)] and simple phobia [OR 5.8 (2.0–16.20]. JH patient with MVP did not present with more anxiety
Bulbena* [32], 2004 Spain	Cross-sectional	Medical department of an auditing consultancy	526 subjects	Anxiety: STAI JH: Hospital del Mar	Males and females with JHS had significantly higher trait anxiety scores (median scores 11, $p < 0.05$; and 17, $p < 0.001$, respectively). Both trait and state anxiety showed significant correlations with JHS (Spearman's rho, 0.10–0.16; $p < 0.05$)
Bulbena* [33], 2006 Spain	Cross-sectional	General population	1,305 subjects	Anxiety: FSS JH: Beighton	JH group had higher fear scores and higher intensity of fears. The association of JH and phobic anxiety might represent a susceptibility factor for these anxiety conditions
Pailhez* [34], 2011 Spain	Cross-sectional	High school students	150 subjects	Anxiety: FSS JH: Hackim and Grahame Others: chocolate rate	Higher fear scores in JH Frequency of chocolate intake higher in JH
Baeza-Velasco* [35], 2009 France	Cross-sectional	Internet survey of tall subjects (>180-cm females and >190-cm males)	158 subjects	Anxiety: LSAS JH: Beighton	High rate of JH and social phobia in tall subjects JH greater social phobia symptoms
Baeza-Velasco* [36], 2010 Chile	Case control	University students	50 JH 50 control	Anxiety: HADS, LSAS JH:	JH group had higher use of antidepressants and anxiolytics compared to the controls. They also exhibited a greater anxiety background, anxiety symptoms and psychosomatic complaints
Baeza-Velasco* [37], 2011 France	Cross-sectional	University students	365 subjects	Anxiety: HADS, LSAS JH: Beighton	JH was associated with higher levels of somatosensory amplification as well was higher scores for depression and general anxiety females
Bulbena* [38], 2011 Spain	Cohort study	General population	137 subjects, followed 15 years	Anxiety: SCID, STAI, ASI, FSS JH: Beighton, Hospital del Mar Other: GHQ 28	JH RR: PD/A: 22 (5-109); Social phobia: 6.5 (1.7–24.2) Simple phobia: 3.3 (1.1–9.6); GAD: 2.9 (0.97–8.6) JH score higher on the social dysfunction subscale and other use of anxiolytics Concordance between the Beighton and Brighton (Kappa = 0.91) and Hospital del Mar (Kappa = 0.61) scales
Baeza-Velasco* [39], 2014 France	Cross-sectional	College students	305 females	Anxiety: STAI JH: self-administered JH Other: alcohol, cigarettes	More tobacco and alcohol if JHS JH higher scores on state anxiety

Table 2. Continued

Study (author/ year/country)	Design	Setting	Sample	Variables studied	Main results
Eccles [40], 2012 UK	Cross-sectional	General population	72 healthy volunteers	Anxiety: BAI JH: Beighton Other: Brain MRI, PBPQ	Amygdala volume greater in JH JH higher scores in interoceptive sensitivity and anxiety JH linked to brain center implicated with emotions and physiological responses

(*) Although most papers came from the same research group, but there is no study duplication. Only Bulbena et al. [31] and Bulbena et al. [33] extracted results from the same sample, but they dealt with different variables.
HADS = hospital anxiety and depression scale; ASI = anxiety severity index; EPQ = Eysenck personality questionnaires; SCID = structured clinical interview for DSM; HAM = Hamilton anxiety and depression scale; ECHO = echocardiogram; NIMH = self-rating scale of mental symptoms; PSS = panic symptom scale checklist; VAS = visual analog scale of anxiety; SCL-90 = symptom checklist 90 R; IBQ = illness behavior questionnaire; SQ = symptom questionnaire; FSF = function symptoms frequency; PAS = panic and agoraphobia scale; STAI = state trait anxiety inventory; SPPI = standardized polyvalent psychiatric interview; LSAS = Liebowitz social anxiety scale; ASP = autonomic symptom profile; QOL = quality of life scale; SF-96 = checklist of individual strength; FSS = fear survey schedule; GHQ = general health questionnaire; BAI = Beck anxiety inventory; SSAS = somatosensory amplification scale; PBPQ = Porges body perception questionnaire.

[34]. Significant differences were found in the severity of fears between the groups with and without hypermobility (7.6 vs. 11; p = 0.001), reinforcing the hypothesis that the intensity of fears is greater in subjects with hypermobility. Only the frequency of chocolate intake was significantly higher among subjects with hypermobility (31.2 vs. 51.2%; p = 0.038) and could correspond to self-treatment of the syndrome.

The relationship between social phobia and height was studied in a cross-sectional study that explored the frequency of social phobia as well as of a heritable disorder of the connective tissue (HDCT) in tall people [35]. One hundred and fifty-eight female subjects with heights greater than 180 cm and male subjects with heights greater than 190 cm were included in the study. Social phobia and HDCT were highly prevalent in tall subjects, and JHS was associated with a greater prevalence of social phobia symptoms.

The association between anxiety disorders and JHS was also assessed in a sample of university students from Chile [36]. Fifty university students with JH and 50 controls were selected to participate in this case-control study. The JH group had higher use of antidepressants and anxiolytics compared to the controls, and they exhibited greater anxiety background, anxiety symptoms and psychosomatic complaints.

A similar study was carried out by Baeza-Velasco et al. on a group of undergraduates in a French university [37]. The aim of this study was to explore the JHS in university students and to assess a possible relationship between this collagen condition and certain psychological variables. Three hundred and sixty-five undergraduates from the French university were included in the study, and the researchers found that JH was present in almost 40% of the sample and was associated with higher levels of somatosensory amplification as well as with higher scores for depression and general anxiety in females.

The first incidence study designed to assess whether JHS is a risk factor for developing anxiety

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disorders was carried out in a 15-year prospective follow-up study by our group [38]. One hundred and fifty-eight individuals without anxiety problems were recruited from a rural town in Spain. JH at baseline was found in 21.1% of the sample, and we found a higher cumulative incidence of panic/agoraphobia disorder in the JH group (41.4%) compared to the control group (1.9%), representing a relative risk of 22.3 [95% CI 4.6–108.7, $p < 0.0001$]. The incidence of simple phobia and social phobia was also significantly higher in the JH group [RR = 6.52, 95% CI 1.7–24.2, $p < 0.001$; and RR = 3.31, 95% CI 1.1–9.6, $p = 0.02$, respectively].

Joint hypermobility has also been assessed in relation to psychoactive substances. Baeza-Velasco [39] designed a cross-sectional study on college students to assess the use of alcohol and tobacco. The odds of being assessed to have JH were greater in those who consumed tobacco and alcohol. Furthermore, women with JH had higher levels of state anxiety and used emotion-focused coping (i.e., efforts to regulate affect) more than any other coping strategies to deal with stress.

The first structural neuroimaging study on this association was published in 2012 and evaluated regional cerebral grey matter in regards to hypermobility status in 72 healthy volunteers [40]. Interestingly, bilateral amygdala volume was higher in the hypermobile group, and their findings linked hypermobility to the structural integrity of a brain center implicated in normal and abnormal emotions and physiological responses. These studies are summarized in table 2.

Reviews

In the last years, several reviews have pointed out and confirmed the association between anxiety disorder and collagen laxity. Garcia-Campayo et al. summarized the articles about the association between JHS and anxiety disorders that were published from their inception to October 2010 [41]. This group reviewed the articles published about JHS and anxiety as well as genetic studies and hypothesized an etiologic explanation for such an association. The most relevant conclusions of the study were that JHS is more prevalent in patients with PA/A and that patients with JHS present a greater prevalence of PD/A. They also found an association between JHS severity and the severity of anxiety symptoms. The authors finally concluded that MVP might play a secondary role in the association of these two variables.

Sanches et al. [42] published the first systematic review on the clinical association between JH and anxiety disorders. This group included articles up to December 2011, and the final study included 17 articles. They found that most of the studies tended to support an association between JH and anxiety disorders, with PD/A being the anxiety disorder most commonly associated with JH. The authors highlighted the need for more research on different anxiety disorders as well as the need of a multidisciplinary approach for the treatment of those patients.

A British group has recently published a systematic review including a meta-analysis, although they used the unspecific title of 'psychological distress' [43]. They included studies that evaluated the prevalence and incidence of 'psychological' conditions for people diagnosed with JHS. The final study included 14 papers and 3,957 participants: 1,006 people with and 2,951 controls without BJHS. The results indicated that people with JH had a higher probability of demonstrating agoraphobia ($p < 0.05$), anxiety (OR 4.39, 95% CI 1.92–10.40), depression (OR 4.10, 95% CI 1.79–9.41) and PDs (OR 6.72, 95% CI 2.22–20.35) than those without JHS ($P < 0.005$). JH was also associated with significantly greater perception of fear and more intense fear ($p < 0.05$). The authors concluded that people with JH commonly exhibit a range of symptoms related to anxiety and depression, and they pointed out that considerable emotional symptoms accompany JHS.

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Finally, Moreno-Peral et al. [44] have just published a systematic review to assess the available evidence on risk factors associated with the onset of PD and Generalized Anxiety Disorder in cohort studies of the general population. PD was associated with age, female gender, few economic resources, smoking and alcohol problems, the number of physical diseases suffered and the JHS.

Psychosomatic Mechanisms Involved

Once the link between anxiety and the Joint Laxity Syndrome is established and their association achieves validity and clinical utility, their common etiological and pathophysiological mechanisms should be identified. Concerning the etiology and the origin of this 'new' revealed condition, so far, only a common genetic linkage has been partially proven. The fact that both conditions (anxiety disorders and joint hyperlaxity syndrome) are highly heritable provides high likelihood for a genetic etiological pathway. In our first genetic study, using pedigree analysis, we found a duplication in chromosome 15 (15q24-q26 named 'DUP25') that appeared to be present in subjects with both conditions. Although replication studies by other research groups failed to confirm this particular duplication, recent studies of the same chromosome showed complex mental and somatic clinical conditions as well as relevant clues for both anxiety (among other features) and morphological anomalies, either in deletion studies [45] or in supernumerary chromosome marker studies [46]. Furthermore, heritability is very often found in both types of patients; it is estimated to be at least 40% in anxiety patients [47], whereas 65% of hypermobile subjects have at least one first-degree relative who suffers from the same condition, albeit it often goes unnoticed.

In regards to the possible pathophysiology of the link between JHS and anxiety, there are two main sources of evidence. First is 'dysautonomia', which is a 'blanket term'-type of disorder that has been related to both conditions. This controversial but successful concept collects a combination of autonomic disorders and, very often, only collections of anxiety symptoms that are simply named differently [48]. On the other hand, the JHS has been repeatedly related to dysautonomia [49, 50].

The second source of evidence for common mechanisms is body awareness, particularly interoception processing. Working together with Prof. Critchley and his group at the Brighton & Sussex Universities, we confirmed a significant correlation between the state anxiety score and joint hypermobility [51]. Interoceptive accuracy was associated with both state anxiety and hypermobility and was formally shown to mediate the relationship between these two conditions. Hypermobile participants, when compared to non-hypermobile individuals, displayed heightened neural reactivity to sad and angry scenes in the brain regions implicated in anxiety states, notably the insular cortex. These findings highlight the dependence of the emotional state on bodily context and increase our understanding of the mechanisms through which vulnerability to anxiety disorders arises in people bearing a heritable variant of collagen.

Toward a New Psychosomatic Phenotype: The Neuroconnective Phenotype

Although there is increasing evidence for somatic comorbidity in the major psychiatric conditions, actual psychiatric classifications do not yet include specific psychiatric illnesses associated with medical conditions other than organic dementias and secondary psychiatric conditions. Apparently two main factors concur for this. First, present nosologies only include two conditions if there is a causal direction between them, for instance, organic brain disorder (dementia) with mental symptoms. Along these lines, concepts like

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vascular depression or even vascular psychiatry are emerging. The reasoning behind this point of view is quite straightforward because it implies the search for etiology and therefore for treatment.

Second, little evidence has shown specific somatic signs or conditions for the description of the present psychiatric illnesses, which has reduced psychiatrists' expectancies to find a coexistence of both, other than the secondary psychosomatic comorbidity. There are already examples of such comorbid situations, like diabetes and schizophrenia, which some have considered part of the same illness [52]. However, the most studied and developed comorbid condition is the JHS in anxiety patients.

When talking about phenotypes in psychiatry, authors tend to include only behavioral and psychopathological traits, which again, represents a bias against somatic or body characteristics. During the first part of the 20th century, one classic part of the clinical assessment that was neglected was the somatotype (i.e., Leptosomatic, Pyknic, Athletic) due to the contributions of Sheldon and Kretschmer. Nevertheless, currently, somatotype is being used in areas of medicine other than psychiatry, notably in Sports Medicine. Our group carried out several studies assessing somatotype in psychiatric samples, and we replicated the findings of the associations between ectomorphic features and anxiety and joint hypermobility twice [22, 23].

However, at the moment, there is no clear nosological place for these coexistent clinical situations. Therefore, there is a need to develop clinical phenotypes containing both psychopathological and somatic features or even proper psychiatric and somatic conditions.

The new phenotype will be built around the core of the association between anxiety disorders (particularly, panic, agoraphobia and social phobia) and the Joint Hypermobility (or better, Hyperlaxity) Syndrome.

The proposed name 'Neuroconnective' for this new phenotype is both comprehensive and specific. It covers the neural component along with the connective dimension of the new phenotype. The prefix *neuro-* refers to the neural basis of the syndrome, which includes the dysfunctional Autonomic Nervous System and enhanced 'body awareness', including interoception, proprioception and exteroception. Furthermore, as a kind of homage, we would like to consider that the *neuro-* prefix also recalls the concept of neurosis, which was a comprehensive category that included both mental and extensive physical symptoms at the same level during the 19th century. 'Connective' refers to the relevant value of the HDCT and to the 'connectivity' between systems, i.e., mind and body.

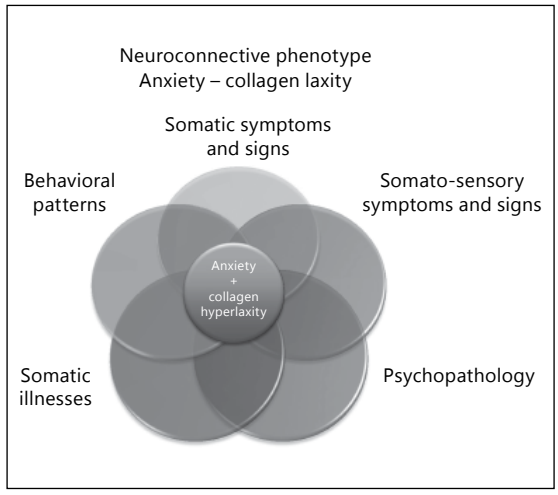

Fig. 1. Diagram of the neuroconnective phenotype with the five components surrounding the core anxiety – collagen laxity.

Therefore, on the basis of the collected genetic, neurophysiological, neuroimaging and most clinical data, several dimensions could be organized in this Neuroconnective model.

The Neuroconnective model is shown in figure 1, in which, around a common core Anxiety-Collagen hyperlaxity, it includes five dimensions: behavioral, psychopathology, somatic symptoms, somatosensory symptoms, and somatic illnesses, with minor overlap.

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Two components appear in the core. The first is anxiety and includes any lifetime presence of panic, agoraphobia, or specific and social phobia. Generalized anxiety should be considered when it has reached great severity or when it is a residual state of any of the previous disorders. The second component of the core is the Joint Hyperlaxity (hypermobility) Syndrome, which could also be classified as EDS type III among the hereditary disorders of the connective tissue.

There is a common characteristic of the components of this core, as very often both go unnoticed and undiagnosed. Failure and delay in initial treatment for patients with anxiety disorders is much higher and longer than in mood disorders [53]. On the other hand, the diagnosis of the JHS is very often neglected, unless there are articular complaints, such as pain, or collateral manifestations, such as sprains or repeated twisted joints.

Each of the following five dimensions includes features that may be present at different degrees and with individual variations. In the content of each dimension, we have included patterns, clinical symptoms, signs and illnesses that appear in these patients. We summarize the main characteristics of each dimension without going into detail because this will be dealt with in a separate paper.

Behavioral dimensions are patterns of defensive mechanisms that are often identifiable at the extreme of a continuous axis. They include active flight or fight (hypervisibility), passive flight or fight (hypovisibility), trophotropism (increased appetite, sleep, social withdrawal, and rest), ergotropism (decreased appetite, weight, but increased activity and aggressiveness), over control (ritualism, compulsions), addictions (alcohol and other nonchemical), restriction (avoidance of spaces, people, activities or delayed use of time, i.e., procrastination) and dependency (of people, spaces, activities).

Somatic symptoms include dysautonomia, asthenic somatotype, dark or 'blue' sclera, 'easy bruising' (especially in women), eczemas, esophageal dyskinesia, sprains and dislocations, viscer-optosis, prolapses, allergies, dyspareunia, and hypertrophic scars or keloids.

The somatosensory symptoms include increased olfactory sensitivity (especially for negative odors), difficulties with eye contact and sensitivity to some luminous stimuli, dizziness (unsteadiness), sighing, dyspnea, dysphagia or choking, palpitations, urologic and vaginal pains (dynias), joint pain (especially cervical or lumbar) and intolerances or enhanced sensitivities to weather, drugs (particularly psychotropic), chemicals, heat or cold.

Psychopathology includes increased exteroception (e.g., meteorosensibility), increased interoception (visceral-body), increased and distorted proprioception, depersonalization, high loss sensitivity, anticipatory anxiety, high positive confrontation (high ability to deal with real acute problems), fear of annihilation or neutralization, fear of rejection, abandonment or neglect, amplification or exaggeration, denial, or avoidance. This dimension could include fears and phobias, including fear of medication (side effects or addiction) and fear of illness or hypochondriasis, and mood disorders (depression and hypomanic states).

Finally, somatic illness includes irritable bowel, dysfunctional esophagus, multiple chemical sensitivity, dizziness or unsteadiness (central vestibular pattern), chronic fatigue, fibromyalgia, glossodynia, vulvodynia, hypothyroidism, asthma, migraines, temporomandibular dysfunction, intolerances to food and drug hypersensitivity.

Some clinical models, particularly the 'Spectrum project' developed by Cassano [54], also propose the inclusion of maladaptive behavioral traits and temperamental traits with features described in the DSM. However, none of these models include the somatic features or conditions included in the Neuroconnective model of illness that is proposed in this paper.

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Conclusions

The well-established association between a collagen condition and anxiety has opened new methods for clinical and basic research. Most probably, new forms of psychosomatic conditions will emerge and different nosological approaches will be required. The Neuroconnective model is a proposal that is being studied and may be useful in clinical practice. Nevertheless, new basic and clinical research on this reviewed association is mandatory because it might open new ways for assessing, understanding and treating patients.

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RESEARCH ARTICLE

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Joint hypermobility is also associated with anxiety disorders in the elderly population

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Background: Anxiety disorders (AD) are very prevalent in the elderly, tend to compromise quality of life, and generate substantial costs. Considering that the prevention and early detection of anxiety may be relevant to increase health gains in older adults, it would be of great interest to identify whether the joint hypermobility syndrome (JHS) is also related to anxiety disorders in this age range.

Methods: Cross-sectional data was collected in a sample of 108 subjects in a rural town in Spain. Instruments included Spielberger STAI, a modified Wolpe Fear Survey Schedule, General health Questionnaire (GHQ)-28, and the anxiety and mood disorders section of the SCID, to assess past year prevalence of anxiety disorders. JHS was evaluated by trained examiners using the "Hospital del Mar criteria".

Results: Among the 108 subjects (55% women, 45% men) over 60 years old, 21.3% meet criteria for JHS. These subjects scored significantly higher in both State ($F = 5.53$; $p = 0.02$) and Trait ($F = 4.68$; $p = 0.03$) anxiety and the GHQ 28 ($F = 6.29$; $p = 0.01$). Compared with non JHS subjects, they had more AD (34.8% vs. 11.8%; $x^2 = 6.90$; $p = 0.02$) and mood disorders (30.4% vs. 10.6%; $x^2 = 5.65$; $p = 0.041$) in the past year prevalence. A multiple logistic regression analysis showed that both JHS ($\beta = 0.196$; $p = 0.04$) and fears ($\beta = 0.34$; $p = 0.001$) are predictors of AD ($r^2 = 188$; $p = 0.001$) in this population.

Conclusions: Joint hypermobility syndrome is associated with anxiety in the elderly population, and it may be used as a physical marker for AD among subjects within this age range.

Key words: joint hypermobility; anxiety; elderly; late life
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Background

Research focused on examining trends of psychiatric disorders among older age groups is limited (Reynolds *et al.,* 2015) but is estimated that by 2050, there will be two billion of older adults globally with a corresponding increase in the number of older adults suffering anxiety disorders (AD)(Blazer, 2003). AD have historically been considered a problem of childhood and early adulthood, with a peak onset between 18 and 40 years. However, later studies demonstrate that the prevalence of AD in community-dwelling older adults is 11%, suggesting a higher prevalence than late-life depression, that is 6% approximately (Beekman *et al.,* 1998; Byers *et al.,* 2010; Reynolds *et al.,* 2015). The prevalence of late-life AD is even higher among homebound elderly nursing homes residents (Junginger *et al.,* 1993), older medical

patients (Tolin *et al.,* 2005), and patients who have chronic medical illness (Stein *et al.,* 1990; Kunik *et al.,* 2005). It is estimated that specific phobia is the most prevalent AD in older life followed by social phobia, generalized anxiety disorder, panic disorder, and agoraphobia (Byers *et al.,* 2010).

Several studies suggest that anxiety has a different presentation among older people as it is often accompanied by co-morbid depression symptoms, and geriatric psychiatry research is struggling to understand the treatment needs of this comorbidity[†] (Byers *et al.,* 2010; Mohlman *et al.,* 2012). For these reasons, AD in late life may be even more likely to be underdiagnosed than in younger groups, but they have a significant impact in terms of health care costs as people with anxiety disorders make heavy use of medical services (Wetherell *et al.,* 2007). AD as a primary cause for hospitalization increase exponentially with age, as do health care costs related to anxiety disorders; the annual US health care costs due to late-life anxiety disorders in 1990 was estimated to be $42.3 billion(Greenberg *et al.,* 1999). AD are also associated with increased depression, decreased quality of life, reduced perceptions of physical and mental health and vitality, greater physical disability, poor quality of life, increased comorbidity, and increased use of health services (Wetherell *et al.,* 2007; Mohlman *et al.,* 2012; Bryant *et al.,* 2013).

The term joint hypermobility syndrome (JHS) was used for the first time in 1967 to describe the association of the joint laxity with some musculoskeletal diseases (Kirk *et al.,* 1967). This syndrome is a highly heritable collagen condition (Ehlers Danlos type III or hypermobile type) and is characterized by an increased distensibility of the joints in passive movements as well as a hypermobility in active movements in the absence of any rheumatologic disease (Hakim and Grahame, 2003). JHS has a strong autonomic pattern; it is more frequent in women (3:1) and has an estimated prevalence of 10–15% in the general population (Hakim *et al.,* 2004), being more prevalent in Asians and Africans compared with Europeans (Hakim and Grahame, 2003). By age groups, it is more common in youngsters and the frequency tends to decrease with age (Wynne-Davies, 1971). As noted in prior studies, the prevalence of JHS decreases in men in the third decade and in women in the fifth decade of life (Wynne-Davies, 1971). JHS has not only articular but also significant extra-articular symptoms such as skin striae, ecchymosis, blue sclera, hernias, prolapses, dysautonomic symptoms, and somatosensory amplifications among others (Mishra *et al.,* 1996; Gazit *et al.,* 2003; Hakim and Grahame, 2004).

The association between JHS and anxiety disorders was described for the first time by Bulbena *et al.* in 1988 in a letter to the *Lancet (*Bulbena et al., 1988*)*. A literature review confirms a strong association between anxiety disorders and JHS(Smith *et al.,* 2014), and there is also limited but growing evidence that this "anxiety/joint hypermobility" entity constitutes a unique phenotype that is seen in other mental illnesses such as depression, eating and neuro-developmental disorders, and alcohol and tobacco misuse (Bulbena *et al.,* 2015). The underlying mechanisms behind this association include genetic risks (Gratacos *et al.,* 2001) autonomic nervous system dysfunction, increased exteroceptive and interoceptive mechanisms, and decreased proprioception (Bulbena *et al.,* 2004b; Mallorqui-Bague *et al.,* 2015; Mallorqui-Bague *et al.,* 2016). Recent neuroimaging studies have also shown an increased response in emotion processing brain areas, which could explain the high affective reactivity seen in those patients (Mallorqui-Bague *et al.,* 2014). Thus, JHS has been proposed as a biological maker for a homogeneous type of anxiety.

Considering that early diagnosis and treatment of anxiety might be relevant to increase health gains in late-life, it would be of great interest to identify specific biological markers of anxiety in that age range. The aim of this study is to evaluate if joint hypermobility in the elderly is also associated with the homogeneous type of anxiety described earlier. In order to this, we characterized the clinical and somatic features of anxiety disorders in this age range and then evaluated if they correlate with JHS.

Methods

The study is part of a large cross-sectional epidemiological study of a rural town in Spain (Portbou, Girona). Subjects that were 60 years old or older were included after the study procedures were fully explained and the informed consent was obtained. The presence of dementia/cognitive impairment, psychotic comorbidities, severe physical (particularly rheumatologic) disease, severe heritable connective tissue disease, and age under 60 years old were the exclusion criteria. The participation of the study was voluntary with no monetary reward, and the study was approved by the local ethics committee. Socio-demographic variables were obtained through direct interview. Clinical measurements were obtained using the following instruments:

- The structured diagnostic interview (SCID) was used to assess anxiety and mood disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria (SCID IV) (First *et al.,* 1995). Major depression, dysthymia, generalized anxiety, panic,agoraphobia, specific phobia and social phobia past year estimated prevalence's were assessed by a trained SCID researcher blind to the joint hypermobility status. Clinical records were also reviewed by an independent psychiatrist blind to the research information to complete the diagnostic information obtained in the interview.
- Joint hypermobility syndrome was evaluated by a trained rater using Hospital del Mar criteria, which is a which is a 10-point cut-off clinical scale with different cut-off points for men and women (3/4 and 4/5) (Bulbena *et al.,* 1992). Because of the age range, a lower cut-off range (1 point lower) was applied to take into account the loss of agility seen in this type of population (2/3 men and 3/4 women).
- Dimensional measures of anxiety symptoms were evaluated using the State-Trait
- Anxiety Inventory (STAI) (Spielberger *et al.,* 1983)
- Fears were evaluated with the modified Wolpe Fear Survey Schedule (mFSS), which is a self-reporting questionnaire that contains a list of the 100 most commonly feared things and situations that are then rated in regards to the intensity of the fear. A modified and validated Spanish version was used (Bulbena *et al.,* 2006).
- To increase the panic screening, we also used the four autonomic questions proposed by Katon developed in 1987(Katon *et al.,* 1987) (1. "Do you ever have sudden episodes of rapid heartbeat or feeling like your heart is pounding?" 2. "Do you ever have sudden episodes of lightheadedness or feeling faint? 3. "Do you ever have sudden episodes of sweating, hot flashes, or trembling?" 4. "Do you every have sudden episodes of chest tightness or a feeling of smothering or not being able to get enough air to breath?" And the panic detection screen question proposed by the National Institute of Mental Health Diagnostic Interview Schedule (DIS) (Robins *et al.,* 1981) ("Have you ever had a spell or attack when suddenly you felt frightened, anxious or very uneasy in situations when most people would not be afraid?")
- Additionally, the General Health Questionnaire-28 (Goldberg, 1978) was used to determine the likelihood of the presence of psychopathology and somatic conditions.

Statistical analysis

Descriptive statistics were used to report the frequencies, means, and standard deviations (SD). Continuous variables were reported as means and standard deviations, and categorical variables were reported as percent (n). Student's t tests and ANOVA were used when comparing for continuous data and $\chi 2$ tests for categorical data. Statistical significance was determined by two-tailed $p < 0.05$. Multiple logistic regression analyses models were used to examine the predictive value of JHS for the diagnosis of anxiety disorders in the sample. All statistical analyses were made using the IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.

Results

The study sample included 108 subjects, 59 women (55%) and 49 men (45%) with no age differences between groups (67. 4 vs. 68.5 years old; $t = 1.029$; $p = 0.306$). Approximately 19% of the sample did work outside their home, 15.7% had been visiting a psychiatrist in the last year (22% of women and 8.2% men; X^2 3.88; $p = 0.0664$), and 22.2% had taken psychotropic drugs (14.3% of men and 28.8% women; X^2 3.27; $p = 0.103$). See Table 1 for complete sociodemographic information.

Twenty-one percent of the sample met Hospital del Mar criteria for joint hypermobility (32.3% of women and 8.2% men; X^2 9.23, $p = 0.004$). Because we were interested in studying the association between anxiety and the joint hypermobility syndrome, several variables were compared between the hypermobile group and the non-hypermobile one, refer to Table 2 for details.

Subjects with JH scored significantly higher in both anxiety state ($F = 5.53$; $p = 0.02$) and trait ($F = 4.68$; $p = 0.03$), GHQ 28 ($F = 6.29$; $p = 0.01$) and also scored higher in the total score of the modified Wolpe Fear Survey Schedule although this did not reach statistical significance ($F = 2.12$; $p = 0.15$).

Table 1 Sociodemographic table

	Men	Women	*p*-value
N = 108	49 (45%)	59 (55%)	—
Age	68.5 years old	67.4 years old	0.306
Psychiatrist visit past year	8.2%	22%	0.064
Psychotropic drugs	14.3%	28.8%	0.103

Table 2 Clinical rating differences between JHS and non JHS groups (* = significant)

Variable	JHS	non JHS	F	*p*-value
STAI-State	30 (±4.6)	26.2 (±7.2)	5.53	**0.02***
STAI-Trait	30.7 (±5.3)	27.8 (±5.6)	4.67	**0.03***
GHQ A (somatic symptoms)	1.70 (±2.3)	1.00 (±1.8)	2.28	0.13
GHQ B (anxiety/ insomnia)	2.13 (±1.9)	1.31 (±1.9)	3.16	0.07
GHQ C (social dysfunction)	0.93 (±1.5)	0.87 (±1.2)	0.03	0.86
GHQ D (depression)	0.74 (±1.7)	0.64 (±1.3)	0.19	0.76
GHQ TOTAL	22.7 (±5.5)	18.6 (±7.2)	6.29	**0.01***
Modified Wolpe Fear Score	134.6 (±51.5)	116.6 (±50.3)	2.12	0.15

JHS, joint hypermobility syndrome; STAI, State-Trait Anxiety Inventory.

We also compared the panic screen question of the DIS with the four autonomic questions proposed by Katon to increase the detection of panic between group, see Table 3 for details. Two questions were answered significantly different when comparing hypermobiles with non-hypermobiles ("Have you ever had a spell or attack when all of the sudden you felt frightened, anxious, or very uneasy in situations when most people would not be afraid?" ($p = 0.019$) and "Have you ever had sudden episodes of palpitations or heart pounding?" ($p = 0.028$)). However, despite the JHS group scored higher in the remaining questions, no significant differences were found between the two groups.

Table 3 Panic screen (DIS and Katon) differences between groups

Panic Screen question	JHS (%)	No JHS (%)	*p*-value
Suddenly feeling frightened anxious, uneasy in situations where others do not? (DIS)	26.1	7.1	**0.019***
Sudden palpitations or heart pounding? (Katon)	60.9	32.9	**0.028***
Sudden lightheadedness or feeling faint? (Katon)	21.7	15.3	0.530
Sudden episodes of sweating, hot flashes, or trembling? (Katon)	26.1	12.9	0.192
Sudden episodes of chest tightness or not being able to obtain enough air? (Katon)	26.1	20.0	0.570

DIS, Diagnostic Interview Schedule; JHS, joint hypermobility syndrome.

Concerning diagnoses, 14.8% of the sample had past year diagnosis of mood disorders (major depression 8.3% and dysthymia 6.48%), and 16.7% of the sample had past year diagnosis of anxiety disorders (7.4% GAD, 3.7% panic or agoraphobia, 2.8% social phobia, and 2.8% specific phobia). Comorbidity between mood and anxiety disorders was frequent; more than half (55.6%) subjects with anxiety had comorbid depression, and almost 70% of the patients with depression (68.7%) were diagnosed also with anxiety disorders. When comparing hypermobiles and non-hypermobiles, the JHS group had higher past year prevalence of anxiety (34.8% vs. 11.8%; $x^2 = 6.90$; $p = 0.02$) and depression (30.4% vs. 10.6%; $x^2 = 5.65$; $p = 0.041$), refer to Table 4 for details. When JHS patients with depression and comorbid anxiety were excluded from the analysis, no significant differences were found between groups for depression (13.0% vs. 2.4%; $x^2 = 4.68$; $p = 0.06$). However, when anxiety without any comorbid depression was compared between groups, the JHS group had significant higher rates of anxiety disorders (21.7% vs. 3.52%, $p = 0.01$), highlighting the solid correlation between anxiety and JHS.

A multiple regression analysis was built to identify the predictive value of JHS for anxiety (see Figure 1) and depression (see Figure 2) in this sample, which was taken as the predicted variable. Besides the JHS, we included as predictors the GHQ-28, the modified Wolpe mFSS, age, and sex. Both joint hypermobility ($\beta = 0.196$; $p = 0.04$) and the mFSS ($\beta = 0.34$; $p = 0.001$) were significantly associated with the diagnosis of anxiety disorders ($r^2 = 188$; $p = 0.001$). However, it did not reach significance for age, sex, and for the GHQ-28. The same mode was built with depression as the predicted variable and was also significant ($r^2 = 132$; $p = 0.01$), but the only predictor that reached significance was the mFSS ($\beta = 0.21$; $p = 0.03$).

Table 4 Past year prevalence differences between JHS and non JHS groups

Diagnosis	JHS (%)	Non JHS (%)	*p*-value
Anxiety with comorbid depression	34.8	11.8	**0.02***
Depression with comorbid anxiety	30.4	10.6	**0.04***
Anxiety without comorbid depression	21.7	3.52	**0.01***
Depression without comorbid anxiety	13.0	2.4	0.06

JHS, joint hypermobility syndrome.

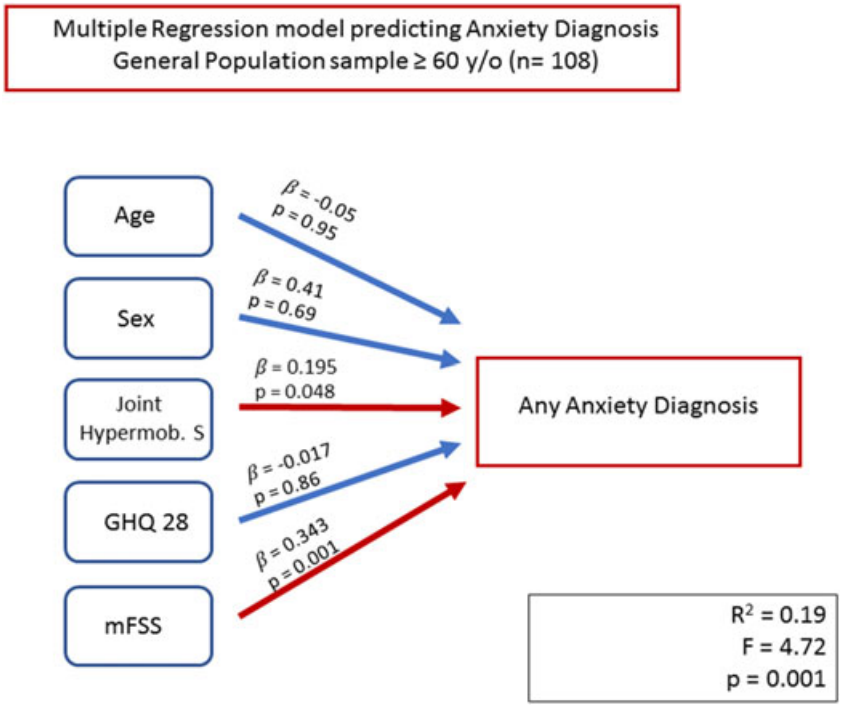

Figure 1 Multiple regression model predicting anxiety disorders in a sample of elderly patients. mFSS, modified Wolpe Fear Survey. [Colour figure can be viewed at wileyonlinelibrary.com]

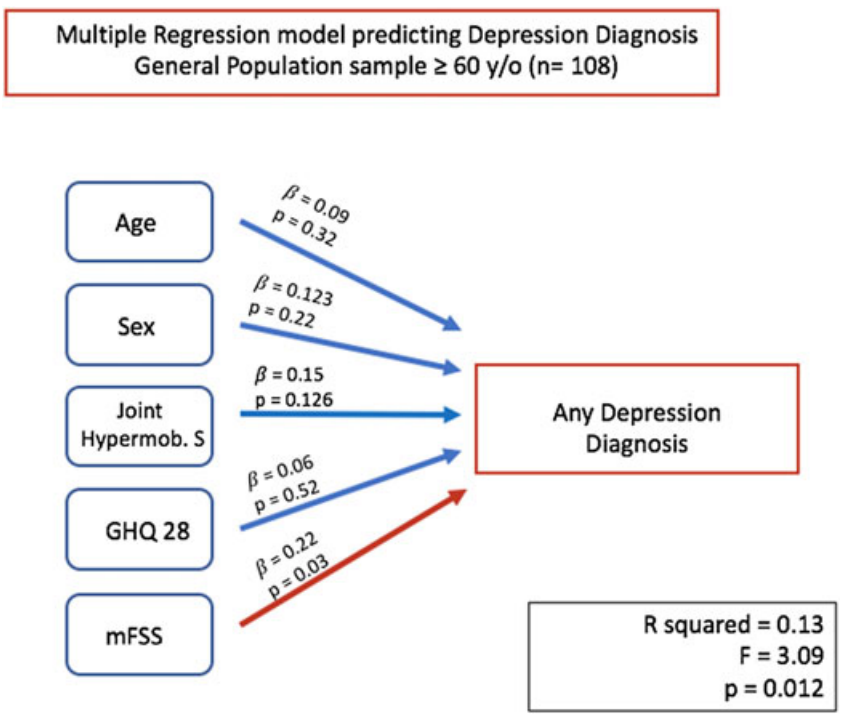

Figure 2 Multiple regression model predicting depression in a sample of elderly patients. mFSS, modified Wolpe Fear Survey. [Colour figure can be viewed at wileyonlinelibrary.com]

Discussion

Anxiety disorders are highly prevalent in later life and have substantial consequences to the individuals and also to the healthcare system but they are often underdiagnosed and untreated. Clinical experience has long suggested that anxiety disorders are heterogeneous syndromes that vary markedly between individuals with respect to their clinical presentations, responses, longitudinal course, and risks of recurrence (Nandi *et al.,* 2009). JHS has been repeatedly associated with AD in clinical (Bulbena *et al.,* 1988; Bulbena *et al.,* 1993; Martin-Santos *et al.,* 1998) and nonclinical populations (Bulbena *et al.,* 2004a), and it can be used as a biological marker for a homogeneous type of anxiety in adults. In this novel study, we assessed if JHS can be used as a biological marker for anxiety in the elderly population. We used both dimensional and categorical instruments to capture subthreshold anxiety symptoms along with measurements of fear, panic, psychopathology, and somatic symptoms.

Literature shows that joint hypermobility tends to decrease with age, and studies that assessed the JH in elder adults used the articular criteria only (Wynne-Davies, 1971), which do not consider the loss of agility secondary to aging. In this study, we evaluated JHS, the multi-systemic condition with "The Hospital del Mar criteria", a more comprehensive scale that includes some extra-articular symptoms that compared with other sets of criteria, have better internal reliability, and homogeneity (Bulbena *et al.,* 1992). Besides this, we modified the cut-off range (1 point lower) to consider the aged population, as the regular cut-off points are usually applied in younger populations only. This may explain the relative high prevalence of JHS found in this sample; however, as expected, it is higher in women than men, which is in line with prior studies.

Subjects with JHS scored higher in the dimensional measurements of anxiety and fears, which is in line prior findings, reinforcing the hypothesis that people with JHS have higher anxiety and intensity of fears. Other studies in non-clinical populations showed that individuals with JHS scored significantly higher in state/trait and social anxiety scales (Bulbena *et al.,* 2004b; Baeza-Velasco *et al.,* 2011). A recent meta-analysis (Smith *et al.,* 2014) revealed that people with hEDS experience significantly greater fear perception and intensity and have higher probability of agoraphobia and panic disorder, which is consistent with our findings. In fact, the only incidence study to date that has evaluated the relationship between anxiety disorders and JHS, has shown that JHS is a risk factor for anxiety disorders after a 15 year follow up (Bulbena *et al.,* 2011).

The multiple regression analysis showed that both JHS and fears were predictors of anxiety disorders, which is consistent with prior studies, but to date this is the first study this in the elderly population. While the correlation between these two variables is well supported by current literature, the evidence about management and treatment of these patients it is still scarce (Bulbena *et al.,* 2017). Future research should further study this correlation to guide for novel therapies for early prevention and treatment. So far, there are no studies evaluating specific pharmacologic treatment for this anxiety phenotype, but Bulbena *et al.* (Bulbena *et al.,* 2017) recently suggested that management of these patients should include psychiatric and psychological approaches coupled with modern physiotherapy.

Diagnostically, the sample had significant differences between the JHS and the non JHS subjects. The JHS group had significantly higher rates of anxiety and depressive disorders, but for this second diagnosis the differences were not significant when patients with depression and comorbid anxiety were excluded from the analysis. This highlights solid correlation between anxiety-JHS that constitutes a specific phenotype that is seen across some psychiatric disorders such as depression, eating disorders, neuro-developmental disorders and substance abuse (Bulbena *et al.,* 2017). The past year prevalence of AD in this sample was 16.7%, and Reynolds *et al.* (2015) recently published a large epidemiological study showing that the past year prevalence of AD tends to decrease by age, being approximately 11.4% in the elderly population with important gender differences. There is a debate whether the prevalence rates of psychiatric disorders increase or decrease with aging; however, the results seem to vary depending on the study design. Small studies small studies reflect an increase an increase of the psychopathology while large epidemiological studies found opposite results. In the study carried out by Reynolds, the analysis was stratified by four different older age groups, being the past year prevalence of AD 14.81% within the age range of 55–65 years old, which is similar to our findings. The small sample size and the relatively young-middle age old participants our study could explain the minor differences.

There are some methodological limitations of the study deserve to be commented. First, sample size was small may not fully represent the general population, and the mean age of the sample was relatively low. Secondly, fears were measured using a self-reported questionnaire, which was intrinsically

subjective, although this situation was identical for subjects with and without joint hypermobility. Thirst, in this study we used DSM-IV criteria for anxiety disorders and those criteria may have been modified in the recently published DSM-V.

In summary, JH is strongly associated with anxiety disorders in the elderly population and can be used as a biological marker for a homogenous type of anxiety in this type of population, which makes a novel contribution to the literature. These results may be a step toward a better understanding of the association between joint hypermobility and anxiety disorders, but further studies are required to further clarify this association.

Conflict of interest

None declared.

Key Points

- Anxiety disorders are very prevalent and underdiagnosed in late life.
- Joint hypermobility and fears are predictors of anxiety disorders in the elderly.
- Joint hypermobility can be used as a biological marker for anxiety disorders in late life as well.

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TITLE: BODY PERCEPTION IN A SAMPLE OF NONCLINICAL YOUNGSTERS WITH JOINT HYPERMOBILITY

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None of the authors have any conflicts of interest.

Keywords: joint hypermobility, anxiety, body perception, autonomic nervous system dysfunction

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ABSTRACT

BACKGROUND: Subjects with Joint Hypermobility Syndrome (JHS) often suffer from anxiety, stress related illness and also from dysautonomia. The autonomic nervous system is hypothesized to play a key role in the relationship between these variables, however, to date, no studies have evaluated body awareness and the reactivity of autonomically-regulated organs in JHS using the Body Perception Questionnaire.

METHOD: A cross sectional study that included 117 nonclinical youngsters (mean age 16.96 ± 0.87 years old) assessed JHS in relation to body perception. The screening of JHS was done using the Self-Reported Screening Questionnaire for Collagen condition and Hypermobility's assessment (SQCH) and body perception was assessed using the Spanish version of the Body Perception Questionnaire (BPQ).

RESULTS: The JHS was found in 33.3% of the sample and it was significantly higher in females (χ^2=12.15; p=<0.001). Subjects with JHS had higher scores in body awareness (p=0.012), stress response (p =0.007), autonomic nervous system reactivity (p=0.01), and in the health history inventory (p =<0.001). In this last subscale, higher frequency of anxiety (p=<0.001), unhappiness (p=<0.001), depression (p=<0.001), bulimia (p=0.012), anorexia (p=0.023), eczema (p=0.003), and severe menstrual cramps (in females only) (p=0.016) were found among the JHS subjects. Moreover, JHS made significantly more visits to mental health professionals (p=0.019) than the non JHS participants.

CONCLUSIONS: Subjects with JHS have a body perception profile characterized by higher body awareness and stress response and greater autonomic nervous system reactivity. They also have higher frequency of anxiety, depression, bulimia, anorexia, unhappiness, severe menstrual cramps (in females only) and eczema. These findings support the hypothesis that the autonomic nervous system and body perception may play a key role in the development of anxiety and somatic illnesses among subjects with JHS, but this needs to be further evaluated in subsequent studies.

INTRODUCTION

The term Joint Hypermobility Syndrome (JHS) is characterized by increased distensibility of the joints in passive movements as well as a hypermobility in active movements along with several extra articular symptoms. The literature shows that JHS is closely associated with anxiety disorders and this correlation constitutes a specific phenotype for a homogeneous type of anxiety in adults and in the elderly (Bulbena-Cabre et al., 2017; Bulbena et al., 2017; Bulbena, Pailhez, Bulbena-Cabre, Mallorqui-Bague, & Baeza-Velasco, 2015). Specifically, JHS has been associated with higher frequency and intensity of fears and greater severity of anxiety, higher somatic complaints and higher frequency of the so-called endogenous anxiety disorders (panic, agoraphobia and social phobia) (Bulbena, Gago, Sperry, & Berge, 2006; Bulbena-Cabre et al., 2016). Moreover, subjects with JHS frequently present with stress-sensitive illnesses such as fibromyalgia, irritable bowel disease, temporomandibular joint disorder and chronic fatigue syndrome (Grahame, 2008).

While the association between anxiety disorders and JHS is well established, the underlying mechanisms are still unclear. Some biological hypotheses have been proposed to explain this association including genetic risks, interceptive sensitivity, somatosensory amplification, emotion processing variances, and autonomic nervous system dysfunction. In the area of genetics, one study found a cytogenetic anomaly (DUP-25) common to these two phenomena (Gratacos et al., 2001) , although to date this study has not been replicated (Henrichsen et al., 2004; Tabiner et al., 2003). The perception and interpretation of physiological excitation plays a role in anxiety disorders (Craig, 2003; Damasio, Everitt, & Bishop, 1996) and JHS subjects have more intense interoception (Mallorqui-Bague et al., 2014) and somatosensory amplification (Baeza-Velasco, Gely-Nargeot, Bulbena-Vilarrasa, & Bravo, 2011). Neuroimaging studies (Eccles et al., 2012; Mallorqui-Bague et al., 2014) have shown significant emotion processing differences in JHS, which could in part explain the vulnerability for anxiety and other somatic symptoms.

Another important biological hypothesis is the autonomic nervous system dysfunction. Dysautonomia have symptoms that overlap with anxiety and JHS. Critchley et al. (Critchley, Eccles, & Garfinkel, 2013) extensively studied visceral inputs because of their influence on thoughts, feelings and behavior. Consistent Chritchley's views, the Polyvagal Theory (Porges, 2011; Porges, 1995) introduced a new perspective relating autonomic function to behavior that included an appreciation of autonomic nervous system as a "system," the identification of neural circuits involved in the regulation of autonomic state that also influence responses to environmental stimuli and an interpretation of autonomic reactivity as adaptive within the context of the phylogeny of the vertebrate autonomic nervous system. Following

this line of research, Porges developed the Body Perception Questionnaire (BPQ), an instrument to assess subjective experiences of body awareness and autonomic reactivity (Porges, 1993). Compared to other scales that measure subjective experiences of body perception, the BPQ was developed with a foundation in the peripheral neural pathways that transmit bodily sensations to the brain, which provides valuable information about the reactivity of autonomically-regulated organs. The BPQ has been used in several peer review studies to obtain objective quantify subjective reports of bodily reactions and states (Critchley, Wiens, Rothstein, & Dolan, 2004; Mehling et al., 2009) but to date this instruments has not been used in JHS.

METHODS

In this study, we evaluated a sample of nonclinical youngsters to assess JHS in relation to the level of awareness of body processes, the subjective experience of autonomic nervous system reactivity, and the frequency of autonomic related illnesses. This cross-sectional study was conducted in a high school in Barcelona (Spain) and a total of 117 subjects (33 males (28.2%) and 84 females (71.7%) with ages ranging from 16-18 y/o were included in the study. All the interested students were selected as eligible and no exclusion criteria were applied. Participation of the study was voluntary without any economic compensation and the informed consent from participants was obtained after the study procedures were fully explained.

Socio-demographic data was obtained through a socio-demographic questionnaire (including visits to Psychiatrist/Psychologist). Among the sample, the mean age was 16.96 (SD± 0.87) years old and 41 (35%) subjects were from 11th grade and 76 (65%) from 12th grade and all of them were Caucasians. In terms of visits to a mental health professional, 32 subjects (27.35%) admitted to seeking mental health help and 85 (72.65%) denied it.

The JHS was screened with the self-reported Screening Questionnaire for Collagen condition and Hypermobility's assessment (SQCH). It is a 7 item questionnaire that includes the basis of the 5 item self-reporting questionnaire of Hakim and Grahame (2003) and 2 extra-articular features (easy bruising and hypertrophic scarring). This questionnaire has adequate clinimetric properties and has been validated for clinical use (Bulbena et al., 2014). The questionnaire is scored by adding the points of each item (ranging from 0 to 7), with cut off scores to diagnose JHS set at ≥3/7.

Body perception was evaluated using the Spanish version of the Body Perception Questionnaire (BPQ). It has a total of 5 dimensions including body awareness (45 items), stress response (10 items), autonomic nervous system (ANS) reactivity (27 items), stress style (12 items, subgroup 1 and 2) and health history inventory (27 items). All ratings except for the Health History Inventory dimension are made on a five-point ordinal scale spanning never (0), occasionally (1), sometimes (2), usually (3), and always (4). The health history inventory also used a five-point ordinal scale but slightly different spanning never (0), mild (1), moderate (2), severe (3) and debilitating (4). Total final score of each dimension is showed as the mean score of each category. The health history inventory included some autonomic-related illnesses including migraine headaches, gastric distress or digestive problems, arthritis, hypertension, hopeless, unhappiness, clinical depression, bulimia, anorexia, obesity, asthma, endocrine problems (e.g., thyroid, adrenal, or gonadal hormone dysfunction), eczema, edema, back problems, diabetes, epilepsy, cancer, hypoglycemia, heart disease, stroke, gastric & duodenal ulcers, psychiatric disorders, pneumonia, heart attack, motion sickness. The following are only for women premenstrual syndrome, severe menstrual cramps and post-partum depression.

Statistical analysis: Descriptive statistics were used to report frequencies, means and standard deviations (SD). The Student tests and ANOVA were used for continuous data and $\chi 2$ tests for qualitative data. Statistical significance was determined by two-tailed $p<0.05$. All statistical analyses were conducted with SPSS – IBM version 22 for Macintosh.

RESULTS

In this sample, 33.3% of the subjects met criteria for JHS (score ≥3/7 SQCH) with a significantly higher proportion of females in this group ($p<0.001$). Based on JHS scores, participants were classified into the JHS and the non JHS groups and different socio-demographic and BPQ variables were compared between these two groups. The JHS group reported significantly more visits to the psychiatrist ($p=0.019$) and scored significantly higher in the Body awareness ($p=0.012$), stress response ($p=0.002$), ANS reactivity ($p=0.01$), and in the health history inventory ($p =<0.001$) compared to the non-JHS group, see full results in table 1.

Table 1 Group differences (JHS vs. non JHS) in socio-demographic and BPQ scores in the sample.

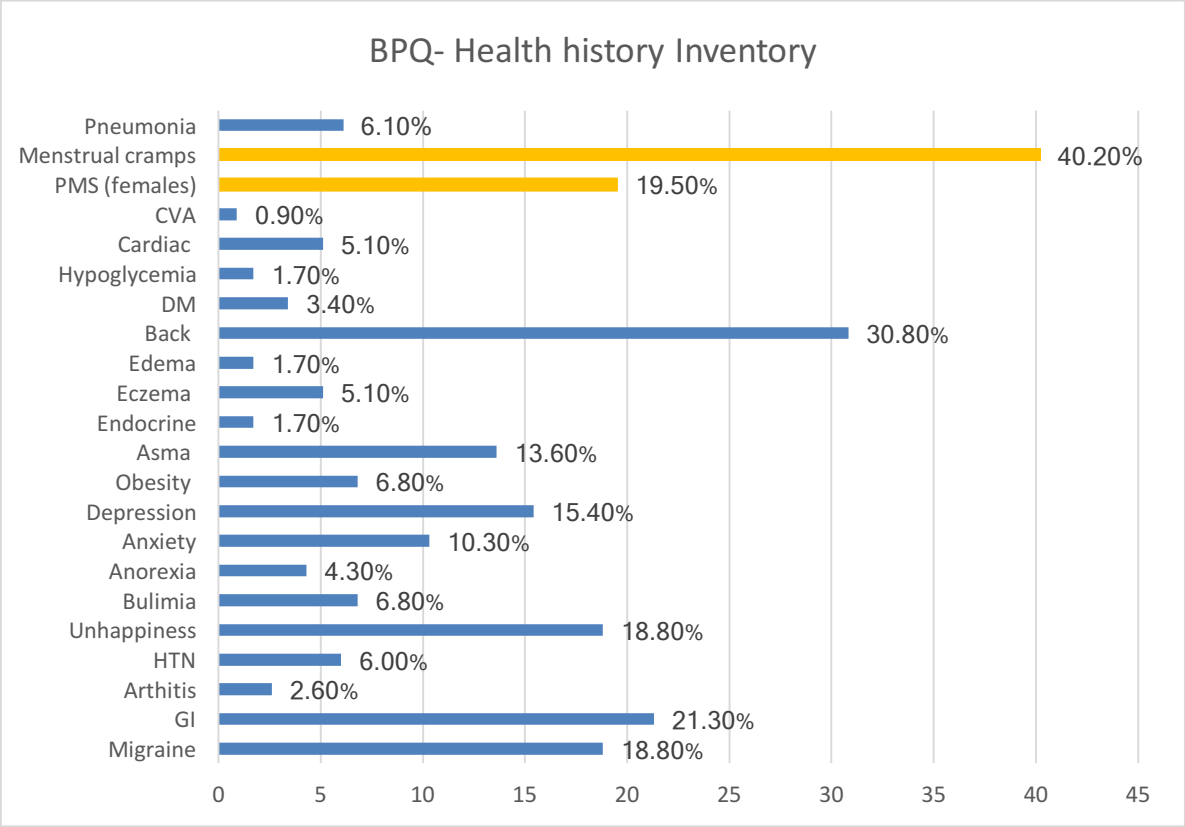
Variable	TOTAL (n=117)	JHS (n=39)	Non JHS (n=78)	Statistical test	*P* value
Psych visits	32 (27.35%)	16 (41%)	16 (21%)	χ^2=5.51	**0.019**
No Psych visits	85 (72.65)	23 (59%)	62 (79%)		
Females	84	36 (92.3%)	48 (61.5%)	χ^2=12.15	**< 0.001**
Males	33	3 (7.7%)	30 (38.5%)		
BPQ- Awareness	2.15±0.50	2.31 ±0.54	2.07±0.41	*t* = 2.56	**0.012**
BPQ- Stress Response	2.21±0.80	2.55 ±0.99	2.05±0.65	***t* = 3.81**	**0.002**
BPQ- ANS reactivity	1.6±0.52	1.77±0.58	1.51±0.45	***t* = 2.61**	**0.010**
BPQ-Stress 1	2.86±0.69	2.91±0.67	2.83±0.70	*t* = 0.63	0.534
BPQ- Stress 2	1.83±1.42	1.88±0.88	1.80±1.62	*t* = 0.31	0.756
BPQ-health history Inventory	6.45±6.37	9.54±6.56	4.88±5.69	*t* = 3.82	**< 0.001**

The health history inventory included some autonomic-related illnesses and the frequencies of each category are shown in Figure 1. The most frequent medical complaints among this nonclinical sample were back problems (30.80%), gastrointestinal problems (21.30%), migraines (18.80%), unhappiness (18.50%), and premenstrual syndrome (19.50%) and menstrual cramps among females (40.20%). The frequencies of each variable of the health history inventory were compared between groups and the JHS subjects had significantly higher percentages of anxiety, depression, unhappiness, bulimia, anorexia, severe menstrual cramps, and eczema as shown in table 2. Non-significant results were not included in the table.

Table 2 Group differences in the health history inventory subscale.

Health Inventory	TOTAL	% JHS	% Non JHS	χ^2	*P* value
Anxiety	10.3%	83.3%	16.7%	15.04	**<0.001**
Depression	15.4%	77.8%	22.2%	18.9	**<0.001**
Unhappiness	18.8%	72.7%	27.3%	18.9	**<0.001**
Bulimia	6.8%	75%	25%	6.71	**0.012**
Anorexia	4.3%	80%	29%	5.12	**0.023**
Severe menstrual cramps	40.2%	51.2%	48.8%	5.72	**0.016**
Eczema	7.7%	77.8%	22.2%	8.6	**0.003**

Figure 1 This figure shows the frequency of each autonomic-related illness measured by the health history inventory in the whole sample.



DISCUSSION

In this novel study, we evaluated JHS and body perception in a sample on nonclinical youngsters in order to define body perception profiles in JHS.

The literature shows that JHS is usually more prevalent in pediatric and young populations ranging from 3-30%. Several factors are known to influence the prevalence old JHS including age, gender and ethnicity (Hakim & Grahame, 2003). In this sample, the prevalence of JHS was slightly higher (33%) which could be explained by the higher frequency of females. The sample was homogenous in terms of age and race but females, besides being overrepresented, were significantly more hypermobiles. This is in line with other studies that have estimated that JHS is more frequent among females (ratio 3:1) (Bulbena et al., 2017).

Subjects with JHS had significantly higher scores in most of the BPQ subscales including body awareness, stress response, reactivity of ANS, and the health history inventory, no significant differences were found in the stress 1 and 2 subscales. The Body Perception Questionnaire was developed to specifically assess subjective experiences of the function and reactivity of target organs and structures that are innervated by the autonomic nervous system. As mentioned above, it is based on the Polyvagal Theory (Porges, 2011; Porges, 2007) which has provided a framework to generate hypotheses regarding the functional organization of the neural pathways that underlie unconsciously-appraised bodily states and their reactivity. The autonomic nervous system has been proposed as one of the key underlying mechanism behind the association between JHS and anxiety. Augmented or disordered awareness of such bodily signals is a feature of multiple clinical disorders such as anxiety, panic attacks, and depression (Cameron, 2001; Domschke, Stevenes, Pfleiderer, & Gerlach, 2010; Wiebking et al., 2015). In JHS, Mallorqui-Bague (Mallorqui-Bague et al., 2014) studied a small sample of healthy volunteers and found that interception sensitivity mediated the relationship between state anxiety and hypermobility.

Following the accumulated evidence on this topic over the past 30 years, our group described the "Neuroconnective phenotype" (Bulbena et al., 2017) in which the solid correlation between JHS and anxiety is in the core and several pathophysiological dimensions are described (somatosensory, psychopathological, somatic illnesses, behavioral patterns, and somatic symptoms domains). Specifically, the somatosensory dimension implies that patients with this phenotype often suffer from dysautonomia and have a greater sensitivity to the inner and external sensory stimuli, and thus, our findings are in agreement with this theory. However, clinical research and treatment often focuses on psychological experiences or brain structures (i.e. amygdala), overlooking the dynamic embodied experiences that are part of affective processes and clinical problems. Subsequent studies should consider the bodily and somatic dimensions along with the psychopathological and cognitive areas of this phenotype for early prevention in order to develop more specific treatments.

Subjects with JHS reported significantly more visits to the mental health professionals and had also significantly higher rates of self-reported anxiety, depression, unhappiness, bulimia, anorexia, severe menstrual cramps, and eczema. Despite we did not assess the prevalence of any psychiatric illness in this sample; the self-reported results on the health history inventory of the participants are congruent with prior research. The anxiety-JHS profile has been proven to be stable across several areas of the psychopathology including depression, substance abuse, eating, and neuro-developmental disorders (Bulbena-Cabre et al., 2016). Therefore, it is not surprising to find that people with JHS seek more

mental health help compared to people without JHS. In terms of eating disorders, subjects with JHS have higher frequency of eating disorders and Baeza-Velasco (Baeza-Velasco, Van den Bossche, Grossin, & Hamonet, 2016; Bulbena et al., 2017) proposed a model of eating disorders in JHS that hypothesized that both articular (i.e. temporomandibular joint dysfunction) and extra-articular features (i.e. gastrointestinal sensitivities, food allergies) play a role in developing and maintaining these eating patterns. The high incidence of food sensitivities among people with JHS is suggestive of histamine hyper-reactivity and several allergic related problems have been described in JHS such as eczema (Hauser & Phillips, 2011). Gynecological aspects of JHS have been largely ignored in the past, but it is now accepted that women with JHS/EDS-HT commonly suffer from irregular menses, meno/metrorrhagias, and severe dysmenorrhea, also known as severe muscle cramps. Together, these findings strengthen the hypothesis that the JHS phenotype constitutes a multisystemic condition and thus a multidimensional approach should be granted in this type of patients.

This study has limitations. First, the study was conducted with a small sample that was homogeneous in terms of race, years of education and age and thus, the results cannot be extrapolated to the entire population. Another limitation is that medical and psychiatric manifestations were based on self-reports instruments and no objective measures were applied to ensure proper validity of the diagnosis.

CONCLUSIONS

Subjects with JHS have an atypical body perception profile characterized by higher awareness, stress response, and ANS reactivity. They also report higher frequency of autonomic related illnesses including anxiety, depression, bulimia, anorexia, unhappiness, severe menstrual cramps (in females only)and eczema and are more likely to seek mental health help compared to controls. These findings support the hypothesis that the autonomic nervous system and body perception may play a key role in the development of anxiety and somatic illnesses among subjects with JHS. The documentation of shared common abnormalities in both the autonomic nervous system and the collagen structure may represent a diathesis not yet identified, but worthy to investigate by subsequent studies.

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