The concomitant diagnosis of fibromyalgia and connective tissue disorders: A systematic review

Najla Alsiri, Meshal Alhadhoud, Tebah Alkatefi and Shea Palmer

Original citation & hyperlink:
Alsiri, N, Alhadhoud, M, Alkatefi, T & Palmer, S 2023, 'The concomitant diagnosis of fibromyalgia and connective tissue disorders: A systematic review', Seminars in Arthritis and Rheumatism, vol. 58, 152127.
https://doi.org/10.1016/j.semarthrit.2022.152127

DOI 10.1016/j.semarthrit.2022.152127
ISSN 0049-0172
ESSN 1532-866X

Publisher: Elsevier

Title Page

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Authors:
Dr. Najla Alsiri. Al-Razi Orthopedics and Rehabilitation hospital. Kuwait.
Dr. Meshal Alhadhoud. Al-Adan hospital, Kuwait.
PT. Tebah Alkatefi. Al-Razi Orthopedics and Rehabilitation hospital. Kuwait.
Prof. Shea Palmer. Centre for Care Excellence, Coventry University and University Hospitals Coventry & Warwickshire NHS Trust, UK.

Corresponding author:

Dr. Najla F. Alsiri. MSc, PhD. Al-Razi Orthopedics and Rehabilitation Hospital, Capital governate, Kuwait.
Tel: 00965-66820032
Email: dr.alsiri@outlook.com

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Summary

Background: Anecdotally, fibromyalgia syndrome (FMS) and connective tissue disorders (hypermobile Ehlers-Danlos Syndrome (hEDS), Hypermobility Spectrum disorders (HSD) and Generalized Joint Hypermobility (GJH)) manifest overlap in their diagnostic approach and symptomatic features. Understanding this overlap is important for accurate diagnosis and the success of subsequent management. This study therefore aimed to identify the prevalence of concomitant diagnosis of FMS and hEDS/HSD/GJH in adults and their shared symptomatic manifestations using a systematic review.

Methods: MEDLINE (via EBSCO host) was systematically searched. Observational research (case-control or single group) studies were considered for inclusion, where adults screened for hEDS/HSD/GJH and FMS were compared in terms of diagnostic prevalence, and musculoskeletal and non-musculoskeletal manifestations. Studies on pediatric populations were excluded. The quality of the included studies was assessed using the National Institute of Health Quality Assessment of Case-Control Studies and Jonna Briggs Critical Appraisal checklist for prevalence studies. The review was registered prospectively in PROSPERO (CRD42020216283).

Findings: The review included eleven studies: nine case-control studies and two single group studies. The prevalence of concomitant diagnosis of hEDS/HSD and FMS ranged from 68%-88.9% and from 8.0-64.2% for GJH and FMS. The prevalence and severity of a range of objective and patient-reported features were similar between hEDS/HSD and FMS, including joint pain (duration, persistence, SF-36-pain component score); joint swelling; muscle weakness; neurological problems; multidimensional pain inventory-activity; dysautonomia and total autonomic symptoms burden (including orthostatic intolerance, reflex syncope, vasomotor, gastrointestinal, diarrhea, constipation and pupillomotor domains); function; and quality of life. Shared symptomatic features between GJH and FMS were mean pain level, tender points count, total myalgia score and psychological impact.

Interpretation: There may be overlapping symptomatology and diagnostic prevalence of FMS and hEDS/HSD/GJH. Clinicians should consider both diagnoses to ensure appropriate diagnosis and management.

Funding: None.

Key words: Fibromyalgia; Hypermobility; Ehlers-Danlos Syndrome.

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1. Introduction:

In the absence of clear understanding of some musculoskeletal conditions and in the presence of similarities of definitions, pathogenesis, and symptomatic features in musculoskeletal practice, it is necessary to understand concomitant diagnoses in potentially overlapping conditions. Fibromyalgia syndrome (FMS) is a musculoskeletal disorder characterized by chronic pain of at least three months duration, which could start as localized pain and progress to widespread lowering of pain thresholds, resulting in widespread tenderness at multiple body sites.[1, 2] FMS is common with a prevalence of 18% (95% CI of 11% - 25%) among people with widespread pain and between 0.2% and 6.6% among the general population.[1-4] The symptomatic features of FMS include headache, sleep disturbances and various syndromes such as myofascial pain, restless leg, irritable bowel, and chronic fatigue and it impacts negatively on psychological health.[2, 5-7]

Hypermobility spectrum disorder (HSD) and hypermobile Ehlers-Danlos Syndrome (hEDS) are chronic musculoskeletal conditions which commonly affect multiple joints.[8-9] Before the 2017 classification framework these conditions were known as joint hypermobility syndrome (JHS) and Ehlers-Danlos Syndrome, Hypermobility Type (EDS-HT).[8] hEDS/HSD are connective tissue disorders, in which the synovial joints demonstrate symptomatic and extraordinary motion due to genetic and pathologic factors in the absence of systemic inflammation.[8-9] The 2017 new classification recognizes 13 subtypes of EDS, but hEDS is the only type with an unknown genetic basis.[9] hEDS/HSD is common with a prevalence of 30% in a musculoskeletal triage service in the United Kingdom and it is more frequent in women.[10-11] hEDS/HSD manifests with multisystemic symptomatic features including migraine headache, fatigue, and sleep, gastrointestinal, autonomic, and psychological disorders.[12-14]

There is a degree of scepticism among medical professionals about hEDS/HSD and FMS, their biomarkers are not reliably identified, and they display an overlap of cardinal symptoms. The pathophysiology of FMS is not clearly understood, and the mechanism of pain is unclear. The existence of joint hypermobility and excessive elastic fibers in patients with FMS have been recognized since the 1980s and 1990s.[15-16] It was previously theorized that joint hypermobility in FMS increased the muscular stress which increased nociceptor excitability, leading to chronicity of pain.[17-18] De Wandele et al., (2014) compared the autonomic symptoms in EDS-HT with other types of EDS and FMS.[6] Patients with joint hypermobility were excluded from the FMS group reaching an exclusion rate of 50%. However, great similarities were still identified between EDS-HT and FMS, in reflex syncope and orthostatic intolerance, vasomotor, secretomotor and gastrointestinal domains.[6] The similarities with FMS were greater than with the other types of EDS.[6] In 2018, Zhang et al., presented a case with a previous diagnosis of FMS, in whom a diagnosis of EDS-HT was later confirmed suggesting a dual diagnosis condition where both FMS and hEDS criteria were met (Figure 1).[19] A major clinical issue is that hEDS/HSD could be overlooked, leading to preferential diagnosis of FMS. The potential for dual diagnosis of both hEDS/HSD and FMS further complicates the clinical decision. Clinicians should be aware of such overlap and consider both FMS and hEDS/HSD during diagnosis.

hEDS/HSD have been described as poorly recognized and managed, under-studied, not well understood and as a human physiology enigma.[20-22] Scheper et al., (2016: p. 12), based on a systematic review exploring the diagnosis and management of JHS, stated: "*The non-identified pathways on which disability overlaps …. limit the ability of health care professionals to provide adequate care."*[22] Indeed, joint hypermobility in hEDS/HSD could be lost in some individuals by the progression of the condition through the three phases of 1) hypermobility, 2) pain then 3) stiffness. This possibility has been recognized in the new HSD classification as 'historical HSD'.[8] Such observations support the complexity of identifying people with hEDS/HSD. A further complication in making an accurate diagnosis and adequately distinguishing between hEDS/HSD and FMS comes from the fact that an individual might have multiple joint hypermobility but it could be asymptomatic. This is known as Generalized Joint Hypermobility (GJH) and its prevalence reached 20% from rheumatology clinic referrals.[23] However, GJH could predispose HSD and overlap with FMS, therefore, the consideration of GJH to understand both hEDS/HSD and FMS is essential.

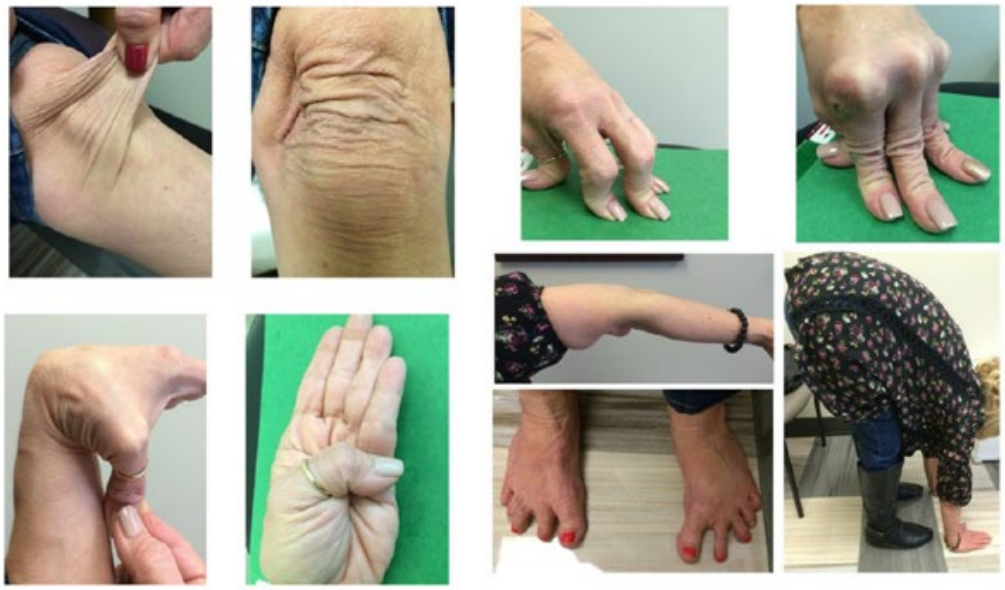


Figure 1: *A patient previously diagnosed with fibromyalgia syndrome. The physical examination showed skin hyperextensibility and generalized joint hypermobility, where the diagnosis of Ehlers-Danlos Syndrome-hypermobility type was then confirmed (adapted with permission from Zhang et al., 2018; Appendix I).*[19]

Various individual primary studies have explored the diagnostic prevalence of FMS, hEDS/HSD and GJH in the same cohort, where varied ranges of diagnostic prevalence and overlap in symptomatic manifestations were identified.[1-2, 5-7, 24-30] The overlap in the symptomatic manifestations of hEDS/HSD and FMS raises the potential risk of misdiagnosis where one diagnosis could be made when the primary problem is the alternative diagnosis. In those cases, the alternative diagnosis might not be considered by the clinician. Yet, there may be another group who genuinely meet the criteria for both diagnoses; dual diagnosis. An accurate diagnosis is needed to ensure appropriately tailored management. However, there is no systematic review exploring the concomitant diagnosis of FMS, hEDS/HSD and GJH to assimilate the previous findings, simplify the complexity of understanding, and reach possible clinical observations and recommendations. The current study hypothesises that the diagnosis of FMS, hEDS/HSD and GJH is highly concomitant.

The study's primary aim is to identify the concomitant diagnosis of FMS and hEDS/HSD in adults in terms of prevalence and shared symptomatic manifestations using a systematic review. A secondary aim is to explore the prevalence and concomitant clinical features of GJH in people diagnosed with FMS.

2. Methods:

2.1 Protocol and registration:

The review was registered in the international Prospective Register of Systematic Review (PROSPERO, CRD42020216283) and conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and relevant guidelines for systematic review.[31-32]

2.2 Eligibility criteria:

Observational research designs of cohort or cross-sectional including case-control and single group designs were considered for inclusion, where hEDS/HSD (or Joint Hypermobility Syndrome (JHS)/ Ehlers-Danlos Syndrome, Hypermobility Type (EDS-HT)), GJH and FMS were compared in terms of prevalence and clinical features. Table 1 details the studied conditions and domains of the review using the DDO components of Domain, Determinant and Outcome.

Table 1: Domain, Determinant and Outcome (DOO) components determined to explore the concomitant diagnosis of fibromyalgia syndrome and connective tissue disorders.	
D: Domain	Adults (≥16 years of age) screened for connective tissue disorders defined as hEDS/HSD (or earlier diagnostic labels of JHS, or EDS-HT). Adults (≥16 years of age) screened for GJH. Adults (≥16 years of age) screened for FMS. Exclusion: Children (<16 years of age).
D: Determinant	'Connective tissue disorders' is defined according to specific international diagnostic criteria (Brighton criteria for JHS; Villefranche criteria for EDS-HT; or Ghent criteria for hEDS or HSD).[8, 9, 21, 33] GJH screened with the Beighton score or alternative measures of hyperlaxity of ≥ 4/9.[34] FMS diagnosed according to the diagnostic criteria of the American College of Rheumatology.[35] Control are adults who do not meet the diagnostic criteria for hEDS/HSD (or JHS/EDS-HT), GJH or FMS.
O: Outcome	The primary outcome is the prevalence of concomitant diagnosis of FMS and hEDS/HSD (or JHS/EDS-HT). Secondary outcome measures are comparisons of clinical features and symptomatic manifestations in hEDS/HSD (or JHS/EDS-HT) and FMS, including both musculoskeletal and non-musculoskeletal involvements. An additional outcome measure is the prevalence of concomitant diagnosis of GJH and FMS and associated clinical features.
Keys: *hEDS refers to Hypermobile Ehlers-Danlos Syndrome, EDS-HT refers to Ehlers Danlos Syndrome Hypermobility Type, FMS refers to Fibromyalgia Syndrome, HSD refers to Hypermobility Spectrum Disorder, JHS refers to Joint Hypermobility Syndrome, and GJH refers to Generalized Joint Hypermobility.*	

2.3 Search strategy and selection criteria:

MEDLINE was the bibliographic electronic database searched via EBSCO host. The search was restricted to peer-reviewed journal articles published in English. The reference lists of the retrieved studies were further screened. The quantity of relevant literature was limited; therefore, no strict exclusion criteria were applied to the initial search strategy to maximize the probability of literature identification. The key terms were "hypermobil*" AND "fibromyalgia" searched on 5 January 2022. The search term "hypermobil*" would cover all hypermobility related conditions including JHS, EDS-HT, hEDS, HSD and GJH, where all diagnostic terminologies of interest incorporate the key term "hypermobil*".[8-9, 21] The key word "fibromyalgia" was selected as it is the only diagnostic terminology used to refer to this condition (Table 2). Employing the selected two key terms aimed to increase the chance of identifying all studies where the two conditions were explored together. Studies not meeting the selection criteria would be excluded at the other stages of the review.

Table 2: History and search details.		
Search	**Query**	**Results**
#3	Search: (fibromyalgia) AND (hypermobil*)	85
#2	Search: fibromyalgia	11,979
#1	Search: hypermobil*	3,477

Two reviewers independently conducted the electronic database searches (NA and TA). The results were compared and checked for errors before a definitive search was conducted and duplicates were removed. The same two reviewers then independently screened titles and abstracts on the basis of the PICO components (Table 1). Results were compared and discussed. If there were any discrepancies, the relevant studies were retained. All remaining studies then underwent independent full text review against the PICO components by the same two reviewers. Discrepancies at this stage were resolved by consulting a third reviewer (MA). Reasons for excluding studies at the full text review stage were recorded (Figure 2). Initial data extraction was conducted by two reviewers (NA and TA) using a standardised pre-piloted form as shown in Table 3, where each reviewer extracted the data independently. Data extraction was then verified by the two reviewers to reach one approved version using the standardized data extraction template (Table 3).

2.4 Data analysis:

Two reviewers assessed the risk of bias independently for each study (NA and TA), and the results were then discussed and agreed. Discrepancy in opinion was resolved by a third reviewer (MA). Two quality assessment tools were used according to the study design. The National Institute of Health (NIH) Quality Assessment tool was used for the assessment of case control studies (Table 4).[36] The tool consists of twelve questions with five possible responses including yes, no, cannot determine, not applicable and not related. Based on the overall score

(0 to 12), the studies were classified as good quality and low risk of bias (≥ 9/12), fair quality and moderate risk of bias (7-8/12), or poor quality and high risk of bias (≤ 6/12).[36] For the studies of single group design, the risk of bias was assessed using the checklist for prevalence studies suggested by the Joanna Briggs Institute. (Table 5)[37-38] The tool consists of nine questions with four possible answers including yes, no, unclear and not applicable. Studies scoring ≥ 7/9 were considered as high quality studies, studies scoring 3-6/9 were considered as moderate quality studies, and studies scoring ≤ 2/9 were considered as low quality studies.[37-38] Inter-rater agreement for critical appraisal of the articles was calculated using % agreement and Cohen's kappa statistic.[39-40] Meta-analysis was not possible due to the heterogeneity between the studies in terms of age range, outcome measures and diagnosis of symptomatic HSD/hEDS and asymptomatic GJH. A narrative synthesis was therefore performed. The results were tabulated to enhance accessibility of the information. All review authors were collaboratively involved with this process of data synthesis.

2.5 Role of funding source:

There was no funding source for this study.

3. Results:

3.1 Study selection:

Eighty-five potential studies were identified through database searching. A total of 61 studies were excluded based on the title and abstract, and 24 studies remained for full text reading. Of these, thirteen studies were excluded.[2, 41-52] The final review included eleven studies.[1, 5-7, 24-30] Figure 2 shows the PRISMA flow diagram outlining the article identification process and eligibility assessment. From the eleven studies; nine studies were categorized as case-control and two studies were characterized as prevalence studies of single group design.

3.2 Study characteristics:

For the purposes of this study the term hEDS/HSD has been used to cover earlier diagnostic categories of JHS and EDS-HT. In terms of the nine case-control studies, four studies focused on hEDS/HSD and five studies focused on GJH (Table 3). The studies focusing on hEDS/HSD, included 974 patients with hEDS/HSD and 686 patients with FMS, compared to 70 healthy controls, 65 patients with rheumatoid arthritis, 11 patients with classical EDS, seven patients with vascular EDS, 6693 patients with spinal pain and 1229 patients with whiplash injury. The studies exploring GJH included 880 patients with GJH, 761 patients with FMS, 266 healthy controls, 1417 patients without GJH, 1532 patients without FMS, 70 patients with other rheumatic diseases, 131 patients with breast implantation, 2369 participants without breast implantation, 341 patients with a diagnosis of connective tissue disorders or rheumatoid arthritis, and 88 patients with widespread pain. In terms of the two single group design studies, one study focused on JHS and one study on GJH. One study included 75 patients with FMS, where 68% of them had JHS.[28] One study included 229 participants, where 50% of them had GJH and 76% had FMS, which indicates that at least 26% of the participants had both GJH and FMS (table 3).[7]

3.3 Risk assessment:

Using the NIH Quality Assessment tool, three studies were rated as poor,[1, 26, 30] four studies were rated as fair,[6, 24, 27, 29] and two studies were rated as good (Table 4).[5, 25] Using the checklist of Joanna Briggs Institute, one study was rated as moderate quality,[28] and one study as high quality (Table 5).[7] Inter-rater agreement was 'substantial' for critical appraisal of the articles using both the NIH tool (82.4% agreement (89/108), $\kappa = 0.723$) and the Joanna Briggs Institute tool (83.3% agreement (15/18), $\kappa = 0.695$).[39-40]

3.4 Results synthesis:

3.4.1 The concomitant diagnosis of connective tissue disorders and FMS:

The concomitant diagnosis of hEDS/HSD, GJH and FMS was determined by seven studies. Two studies explored the prevalence of hEDS/HSD and FMS,[28-29] while five studies explored the prevalence of GJH and FMS.[1, 5, 24-26] All the studies estimated the prevalence figure by using the number of cases with hEDS/HSD or GJH as the numerator relative to the number of cases with FMS as the denominator except one study who estimated the prevalence figure by using the number of cases with FMS as the numerator relative to the number of cases with JHS/EDS-HT as the denominator.[29] The prevalence of the concomitant diagnosis of hEDS/HSD and FMS showed high figures. In a single group design study, 68% of the patients with FMS were diagnosed with JHS using the Brighton criteria, which was rated as a moderate quality study (Table 5).[28] 88.9% of JHS/EDS-HT patients met the criteria for FMS using the Villefranche/Brighton criteria, which was rated as fair (Table 4).[29] One study enrolled women and men,[29] while one study enrolled only women.[28] One study recruited the patients from an outpatient clinic for heritable connective tissue disorders.[29] The setting of the study was not mentioned by Kozangolu et al., (2015) (Table 3).[28]

The prevalence of the concomitant diagnosis of GJH and FMS were specified by five studies ranging from 8.0% to 64.2%. The lowest GJH prevalence figure was 8% of participants with FMS and 6% of participants without FMS ($p > 0.05$).[24] A higher prevalence figure was determined, where 27.3% of people with FMS had joint hyperlaxity compared to 11.4% in people with another rheumatic disorders ($p < 0.05$).[1] An even higher prevalence was identified, where 46.6% of the FMS group had GJH compared to 28.8% in the control group ($p<0.05$).[5] A 64.2% prevalence of GJH was highlighted in patients with FMS, and 22% in the control group ($p<0.05$).[26] One

study explored the association between hypermobility and FMS but did not present a specific percentage, but patients with FMS were found more than twice as likely to have GJH than patients without FMS ($p<0.001$), and a significant association was identified between GJH and FMS ($p = 0.0001$) (Table 3).[25] Two studies were rated as good quality where the identified prevalence figure for GJH in people with FMS was 46.6%, and a significant association was identified between GJH and FMS.[5, 25] One study was rated as fair and reported a prevalence of GJH in FMS of 8%.[24] Two studies were rated as poor-quality studies and the reported prevalence of GJH in FMS was 27.3% and 64.2%, respectively.[1, 26] Four studies enrolled only women,[1,5,24,25] while one study enrolled women and men (Table 3, 4 and 5).[26] The setting of the study was specified by two studies, one study recruited the participants from a University, and one study recruited the participants from a single rheumatology practice.[5, 25]

3.4.2 The concomitant symptomatic features in hEDS/HSD, GJH and FMS:

a) Pain:

Pain was explored by three studies.[5, 27, 30] One study explored pain in GJH,[5] and two studies explored pain in EDS-HT.[27, 30] The first study was rated as good, where mean pain level, tender points count and total myalgia score were not statistically different between FMS cases with and without GJH.[5] A fair rated study found no significant difference between patients with FMS and EDS-HT in joint pain, however headache, muscle pain and pain severity were significantly higher in the FMS group compared to the EDS-HT group.[27] One poor rated study reported no significant differences between the EDS-HT and FMS groups in pain duration and multidimensional pain inventory-activity.[30] Comparable percentages of persistent pain were specified for the EDS-HT group (88.9%), and for the FMS group (91.3%), and no significant differences were found between the groups in the SF-36-pain component score.[30] In contrast, significant increases were found in the FMS compared to EDS-HT in numerical rating scale, multidimensional pain inventory; pain severity, distress and interference, and the number of painful regions, while the multidimensional pain inventory-control subscale was significantly higher in the EDS-HT compared to FMS (Table 3 and 4).[30]

b) Joint instability:

One fair rated study explored joint dislocation and distortions, pelvis instability and snapping, and joint locking, where symptoms of joint instability were found to be significantly higher in the EDS-HT group compared to the FMS group (Table 3 and 4).[27]

c) Autonomic symptoms:

Two studies examined the autonomic symptoms profile in EDS-HT and FMS where both were rated as fair methodological quality.[6, 27] No significant difference was found between EDS-HT and FMS in dysautonomia.[27] The EDS-HT group showed similar total autonomic symptoms burden compared to the FMS group including the domains of orthostatic intolerance, reflex syncope, vasomotor, gastrointestinal, diarrhea and constipation and pupillomotor.[6] Yet, EDS-HT showed significant problems in bladder function ($p<0.001$) and scored less in the domain of sleep dysfunction ($p = 0.007$) when compared to FMS.[6]

d) Mitral valve prolapse:

One moderate quality study suggested that the prevalence of mitral valve prolapse significantly increased in patients with FMS when they meet the diagnosis of JHS.[28] The frequencies of mitral valve prolapse and JHS were higher among patients with FMS compared to the general population prevalence ($p = 0.000$). JHS in patients with FMS was found to increase the risk of mitral valve prolapse about ninefold compared to patients with FMS without JHS (Table 3 and 5).[28]

e) Myalgic encephalomyelitis/ chronic fatigue syndrome:

A high quality study explored patients with myalgic encephalomyelitis/ chronic fatigue syndrome and considered both GJH and FMS.[7] 50% of the patients with myalgic encephalomyelitis/ chronic fatigue syndrome were found to have GJH, 20% were found to have hEDS, and 76% were found to have FMS (Table 3 and 5).[7]

f) Other symptoms:

A range of other symptoms were reported by a fair quality study.[27] No significant differences were identified between the EDS-HT and FMS group in joint swelling, muscle weakness, neurological problems and functional impairment measured with the sickness impact profile (Table 3 and 4).[27] Yet, the FMS group had significantly higher fatigue and muscle stiffness compared to the EDS-HT, while the EDS-HT group complained of significantly higher muscle cramps, tendinitis and skin problems compared to the FMS group.[27]

g) Psychological impact:

The psychological impact was examined by three studies.[5, 27, 30] A good quality study found no statistically significant difference for those with and without GJH when all have FMS.[5] However, a fair quality study identified statistically greater cognitive and emotional problems, and psychological impairment in daily life in the FMS group compared to EDS-HT.[27] Similarly, a poor rated study, found significant differences between EDS-HT and FMS group in the Hospital Anxiety and Depression Scale and the SF-36-mental component score, indicating more psychological impact upon the FMS group compared to the EDS-HT group (Table 3 and 4).[30]

h) Sleep disturbances:

Two studies analyzed sleep disturbances, where both were rated as fair studies.[6, 27] Patients with FMS had significantly higher problems with sleep compared to EDS-HT ($p<0.001$).[27] Similarly, FMS patients have more sleep dysfunction compared to the EDS-HT patients ($p = 0.007$) (Table 3 and 4).[4]

i) Quality of life:

Quality of life was explored by one study, which was rated as poor quality, suggesting no significant difference between the EDS-HT and FMS groups using the European Quality of Life Index.[30]

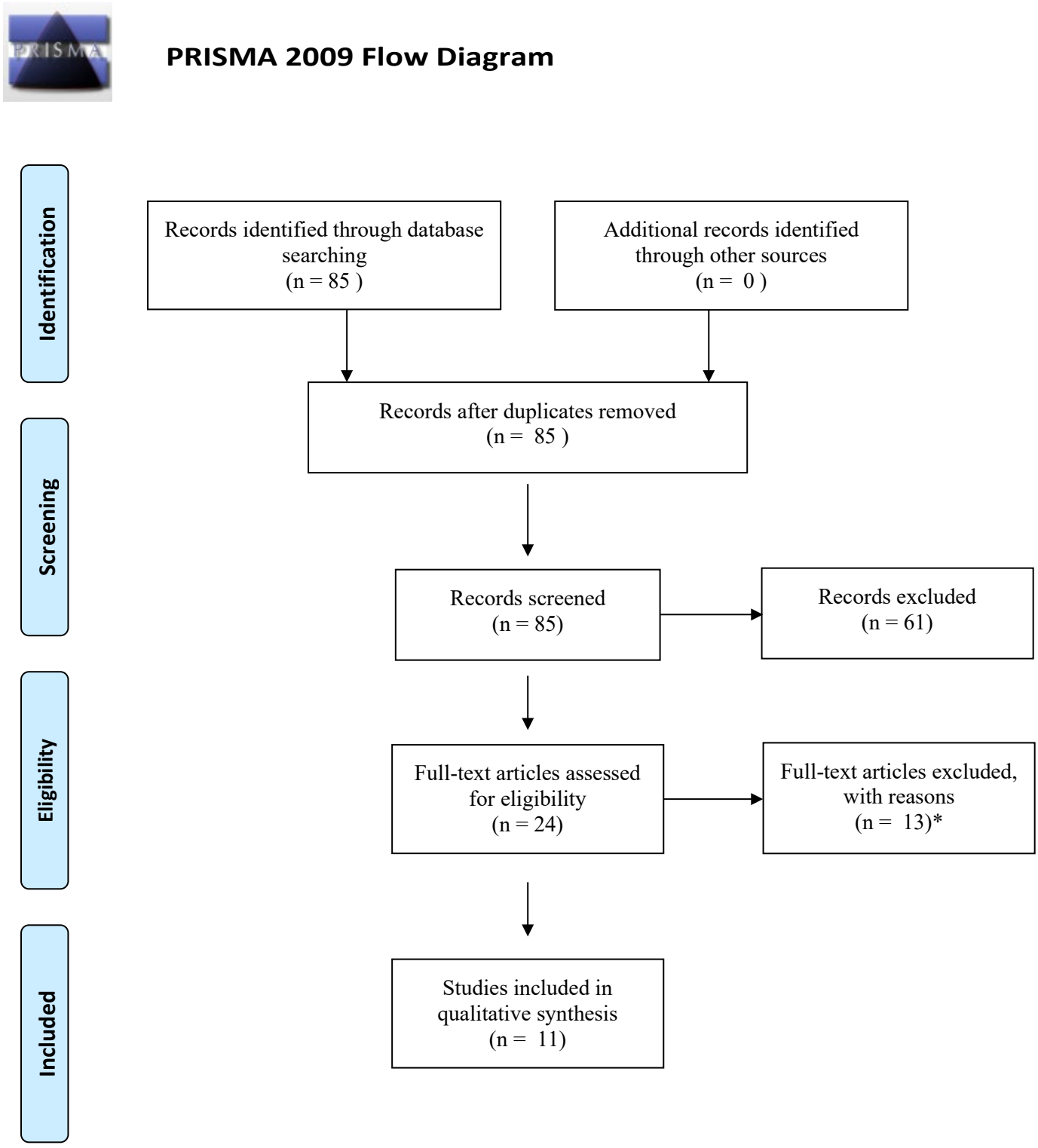


Figure 2: A flow diagram of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) outlining the article identification process.[32]

**Excluded articles with reasons after full text reading: three studies were not related to the specific scope of the study;* [43, 47, 50] *one study presented pediatric data;*[47] *five articles were descriptive studies using the previous literatures;*[41-42,46-48,51] *two papers were letters to the editor;*[44-45] *one study for not specifying the diagnostic criteria for fibromyalgia syndrome;*[2] *and one study because not all the included participants were diagnosed with fibromyalgia syndrome.*[52]

Table 3: The characteristics of the reviewed studies exploring both fibromyalgia syndrome and connective tissue disorders.								
Study	**Purpose**	**Study design**	**Participants; number, age and sex**	**Setting (location) clinic/ hospital country**	**Diagnostic criteria**	**Outcome measure**	**Main results**	**Secondary Results**
Case-control studies								
HSD/ hEDS/ JHS/ EDS-HT								
Rombaut et al., (2011)[27]	Investigate functional impairment and the impact of pain in patients with EDS-HT, and compare the burden of disease in women with FMS and RA.	Comparative study	206 female patients: -72 with EDS-HT (age 40.1 ± 11.94 years). -69 with FMS (age 44.3 ± 9.88 years). -65 with RA (age 54.9 ± 12.12 years).	Centre of Medical Genetics at Ghent University Hospital: -FMS patients from the outpatient Department of Physical and Rehabilitation Medicine. -RA patients from the Department of Rheumatology.	-Revised Villefranche criteria for classification of EDS-HT. -1990 American College of Rheumatology diagnostic criteria for FMS.	-Sickness Impact Profile (SIP) for functional impairment. -Multidimensional Pain Inventory for psychological impact of chronic pain. -Type, prevalence, and severity of symptoms by using two open ended question.	-Sickness Impact Profile in EDS-HT was 19.8 ± 11.87 and 22.3 ± 10.44 in FMS group, which was not statistically significant. -Sickness Impact Profile results showed clinically relevant health related dysfunction in all groups. -The EDS-HT group reported similar physical and overall function, but better psychological function compared to the FMS group.	-EDS-HT group was at similar age to FMS group. -The EDS-HT group showed significantly lower levels of pain severity, life interference and effective distress in comparison with the FMS group. -Social support for help in coping with pain was similar between the EDS-HT and FMS groups. -EDS-HT is associated with a consistent burden of disease similar to that of FMS.
De Wandele et al., (2014)[6]	Gain insight into the autonomic symptom profile in EDS-HT, and to compare autonomic symptoms in EDS-HT with other types of EDS i.e., the classical and vascular types and with FMS and healthy controls.	Control study	179 patients (157 women and 22 men): -80 patients with EDS-HT (age 40.7 ± 12.16 years, 93.8%, females). -11 patients with classical EDS (age 32.3 ± 14.35 years, 63.6% females). -7 patients with vascular EDS (age 37.2 ± 9.36 years, 50.0% females). -38 patients with FMS (age 47.6 ± 8.76 years, 100.0% females). -43 healthy controls (age 38.4 ± 9.91 years, 79.1% females).	-EDS patients from the Centre for Medical Genetics at Ghent University Hospital. -FMS patients from the outpatient Department of Physical and Rehabilitation Medicine at Ghent University Hospital.	-EDS diagnosis according to the Villefranche Nosology. -FMS patients according to 2010 American College of Rheumatology diagnostic criteria.	-Autonomic symptom profile. -SF-36 -5-point hypermobility questionnaire. -Individual strength. -Pain detect questionnaire. -Hospital anxiety and depression scale. -Baecke questionnaire.	The total autonomic burden was statistically significantly higher in EDS-HT (57.9 ± 21.57) than in controls (11.3 ± 19.22), cEDS (32.3 ± 19.47), and vEDS (29.1 ± 19.18) (all ps <0.001), but comparable to FMS (53.8 ± 19.85).	-Orthostatic and gastrointestinal complaints were prevalent. -The correlation of Generalized Hypermobility Questionnaire (r = 0.298) and Pain Detect Questionnaire (r = 0.413) with the Autonomic Symptoms Profile supports the hypothesis that joint hypermobility and neuropathy may play a role in the development of autonomic symptoms. -Hypermobile patients were excluded from the FMS group if they fulfilled one or more of the following minor criteria for EDS-HT including: recurrent joint dislocations, and/or a positive family history for hypermobility/joint dislocations
Di Stefano et al., (2016)[29]	Collecting information on the mechanism underlying pain related to JHS/EDS-HT, verifying whether this symptom depends on somatosensory nervous system damage or central sensitization.	Control prospective study	-27 consecutive patients with JHS/EDS-HT (3 men and 24 women, age 35.7 ± 10.9 years). -27 healthy volunteers (3 men and 24 women, age 35.0 ± 11.1 years).	-Outpatient clinic for heritable connective tissue disorders at the Physical Medicine and Rehabilitation Unit at Sapienza University, Rome. -Controls from the hospital staff matching with age and gender.	-Villefranche criteria for EDS-HT -Brighton criteria for JHS. -Fibromyalgia diagnosed according to the preliminary Diagnostic Criteria for FMS established by 2010 American College of Rheumatology diagnostic criteria.	-Neuropathic pain questionnaire DN4. -FMS rapid screening tool. -Quantitative sensory testing methods: thermal-pain perceptive thresholds and the wind-up ratio and recorded a standard nerve conduction study to assess non-nociceptive fibers and laser-evoked potentials, assessing nociceptive fibers, motor conduction study.	-Neurological examination showed unremarkable findings. -Sensory profiling showed no sensory deficits. -Most patients suffered from widespread pain. -Patients with JHS/EDS-HT had hyperalgesia to cold and heat stimuli, having lowered cold and heat pain thresholds ($p < 0.001$) and an increased wind-up ratio ($p < 0.001$).	The study enrolled 27 patients with JHS/EDS-HT, 24 patients were compatible with FMS using the FMS rapid screening tool.
Molander et al., (2020)[30]	Comparing EDS and hypermobility syndrome with FMS with respect to patient reported outcome measures.	Comparative study of multiple group	-EDS/HMS group = 795 patients, (93.6% women, age 35.97 ± 10.81 years). -FMS group = 579 patients, (95.1% women, age 43.57 ± 10.34 years).	Swedish Quality Registry for Pain Rehabilitation.	-Fibromyalgia diagnosed according to the American College of Rheumatology	-Numeric Rating Scale. -Multidimensional Pain Inventory.	-EDS/HMS: 88.9% persistent pain. -FMS: 91.3% persistent pain. -Statistically significant differences between EDS/HMS and FMS group in age, Numerical Rating Scale, Multidimensional Pain Inventory-	No differences were found between the EDS and hypermobility syndrome group in clinical features and demographics, so both were clustered

			-Spinal pain group = 6693 patients, (60.3% women, age 46.63 ± 11.13 years). -Whiplash associated disorders group = 1229 patients (60.4% women, age 39.4 ± 10.59 years).		diagnostic criteria for FMS.*+ -EDS were diagnosed according to the Villefranche nosology for EDS.*	-Single question about pain duration, pain regions. -Emotional distress using Hospital Anxiety and Depression Scale. -Life impact: health-related quality of life using the Short Form Health Survey (SF36) and European Quality of Life Instrument (EQ-5D).	pain severity-distress-interference-control, number of pain region, Hospital Anxiety and Depression Scale, SF-36-mental component score, European Quality of Life-VAS (all ps < 0.001). -No significant differences between EDS/HSD and FMS in pain duration, SF36-vitality, Multidimensional Pain Inventory-Activity, SF36-Physical Component Score, European Quality of Life Index.	in one group named EDS/HMS resulting in a group of 795 patients.
GJH								
Acasuso-Díaz and Collantes-Estévez (1998)[1]	Test the hypothesis that joint hypermobility can play some role in the pathogenesis of pain in primary FMS.	Control study	-66 women with FMS (age 36.8 years). -70 control women with other rheumatic diseases (age 31.6 years). -Those over 50 years of age were excluded.	Not mentioned	-1990 American College of Rheumatology diagnostic criteria for FMS. -The Non-Dominant Spanish modification for hyperlaxity.	-Tender points. -Pain. -Digital palpation of 4 kg weight.	-27.3% of women with FMS had joint hyperlaxity, while 11.4% of women with another rheumatic disorders had joint hyperlaxity (p < 0.05).	----
Ofluoglu et al., (2006)[26]	Determine the coexistence of hypermobility and FMS in women.	Control study	-93 women with FMS (age 43.5 ± 9.9 years). -58 healthy women without FS (age 40.2 ± 11.1 years).	Not mentioned	-American College of Rheumatology criteria for FMS.+ -GJH identified as Beighton score ≥ 4/9.	Widespread soft tissue pain using visual analogue scale.	-Beighton score for FMS was 4.7 ± 2.1, and 2.9 ± 2.4 for the control group (p < 0.0001). -The frequency of GJH was 64.2 % in the FMS group, and 22% in the control group (p < 0.05).	Negative correlations were found between the Beighton score and age (r = -0.42, p < 0.001), and number of trigger points (r = -0.24, p = 0.03) in all patients.
Sendur, Gurer and Bozbas (2007)[5]	Determine the frequency of hypermobility in FMS patients in relation with clinical findings.	Control study	236 women; -118 with FMS (age 47.69 ± 10.98 years). -118 as control (age 46.08 ± 10.85 years).	Fibromyalgia clinic of the Physical Therapy and Rehabilitation Department of the Adnan Medderes University.	-GJH identified as Beighton score ≥ 4/9. -1990 American College of Rheumatology diagnostic criteria for FMS.	-Visual Analogue Scale for pain. -Turkish version of the FMS Impact Questionnaire to determine the health status. -Tender points. -Total myalgic score.	-46.6% of the FMS group had GJH, 28.8% in the control group had GJH (p < 0.05). -Mean Beighton score was 3.68 and 2.55 for the FMS and the control group, respectively (p < 0.001).	-More severe clinical findings were observed in the FMS patients with GJH when compared with ones without. -No statistically significant differences were observed between FMS cases with and without GJH (p>0.05) in regard to outcomes of clinical findings (mean pain level, tender points count, total myalgia score, and Fibromyalgia Impact Questionnaire score).
Lai et al., (2000)[25]	Examine possible relationships among FMS, hypermobility, and breast implants.	Comparative two group design	Medical records of 2500 female patients ages 25-65 years: -484 patients with FMS. -1532 patients without any evidence of FMS. -880 patients with GJH. -1417 patients without GJH. -131 patients with breast implants. -2369 patients without breast implants. -341 patients have a diagnosis of connective tissue disorders or RA.	Single rheumatology practice in Atlanta, Georgia.	- 1990 American College of Rheumatology diagnostic criteria for FMS. -GJH defined as Beighton score greater than 3/9.	----	-Patients with FMS were more than twice as likely (OR 2.05, 95% CI 1.64-2.55, p < 0.001) to have GJH than patients without FMS. After adjustment for age, income, presence of connective tissue disorders or RA, and implants OR increased to 2.20 (p < 0.001). -Statistically significant associations were found between GJH and FMS (adjusted OR 2.20, 95% CI 1.73 - 2.80, p = 0.0001), and between GJH and breast implantation (adjusted OR 1.80, 95% CI 1.19, 2.69, p = 0.0005).	----
Karaaslan, Hazendaroglu and Ozturk (2000)[24]	Investigate the association of joint hypermobility and primary FMS.	Comparative control design	-88 patients with widespread pain (females, median age 34 years). -90 healthy controls (females, median age 36 years).	Patients admitted to rheumatology department.	-1990 American College of Rheumatology diagnostic criteria for FMS. -Beighton hypermobility score of ≥ 4/9.	----	-Fifty-six patients meet the FMS diagnostic criteria. -6 of the 90 healthy controls meet the diagnostic criteria for FMS. -The frequency of joint hypermobility was 8% in patients with FMS and 6% in subjects without FMS (p>0.05). -16% of the patients evaluated with widespread pain had joint hypermobility.	-Joint hypermobility was found in 10 of 32 FMS patients (31%) who had not exactly met the FMS diagnostic criteria. -The occurrence of joint hypermobility was more common in FMS patients compared to controls (p < 0.001).

Prevalence Single Group Studies								
JHS/ HSD/ EDS-HT								
Kozangolu et al., (2015)[28]	Determine whether benign joint hypermobility syndrome modified the risk of mitral valve prolapse in patients with FS.	Single group	-75 females with FMS (age 36.7 ± 10.0 years).	Not mentioned	-1990 American College of Rheumatology diagnostic criteria for FMS. -Beighton and Brighton criteria for joint hypermobility and benign hypermobility syndrome.	-Echocardiographic evaluation for mitral valve prolapse. -Pain measured with visual analogue scale.	-68% of the FMS patients diagnosed with benign JHS. -20% of the FMS patients had mitral valve prolapse. -Visual analogue scale for pain was 61.1 ± 16.5.	The frequency of mitral valve prolapse was significantly higher in patients with benign JHS than in patients without (p = 0.028).
GJH								
Bragée et al., (2020)[7]	Test the hypothesis that hypermobility signs of intracranial hypertension, and cranio-cervical obstructions maybe overrepresented in patients with Myalgic encephalomyelitis/ chronic fatigue syndrome.	Single group retrospective design	229 participants: -190 women (age 45 years). -39 males (age 44 years).	Specialist clinic for referred patients with severe Myalgic encephalomyelitis/ chronic fatigue syndrome.	-Myalgic encephalomyelitis/ chronic fatigue syndrome as defined by the Canada Consensus Criteria. -Hypermobility using the Beighton Score with five or more indicating hypermobility. -Allodynia with quantitative sensory testing for pain in 18 areas indicative of fibromyalgia syndrome. -FMS diagnosed with 1990 American college of Rheumatology diagnostic criteria.	-Intracranial hypertension measured with quotient of the optic nerve sheath diameter/ eyeball transverse diameter on both sides using magnetic resonance imaging of the brain. -Cerebellar tonsil position in relation to the McRae line, indicating foramen magnum. -Cranio-cervical obstructions with MRI of the cervical spine.	-115 (50%) had GJH. -44 (20%) had hEDS. -173 (76%) had FMS. -55% of 205 patients who did the MRI had increased optic nerve sheath diameter, and 83% has signs of possible intracranial hypertension. -56% had cerebellar tonsils protruding under the McRae line into the foramen magnum. -80% of 125 who did cervical spine MRI had craniocervical hypertension. -96% had allodynia.	-Optic nerve sheath diameter values of > 5.8 mm; indicating intracranial hypertension were found in a majority of the participants. -This study was not used to determine the contaminant diagnostic figure but to highlight a common symptomatic feature because the main sample is diagnosed with Myalgic encephalomyelitis/ chronic fatigue syndrome, and not with FMS, hEDS or FMS. -It has been included to highlight that ME/CFS is common in GJH, hEDS and FMS.

Key: FMS: Fibromyalgia syndrome, EDS: Ehlers-Danlos Syndrome, EDS-HT: Ehlers-Danlos Syndrome Hypermobility type, RA: Rheumatoid Arthritis. Figures are mean ± standard deviation, except where specified otherwise.
****Information was requested from Author.***
+The version of the FMS diagnostic criteria was not specified.

Table 4: The National Institutes of Health (NIH) Quality Assessment tool of Case-Control Studies.														
Study		**1.Was the research question or objective in this paper clearly stated and appropriate?**	**2.Was the study population clearly specified and defined?**	**3.Did the authors include a sample size justification?**	**4.Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?**	**5.Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or selected cases and controls valid, reliable and implemented consistently across all study participants?**	**6.Were the cases clearly defined and differentiated from controls?**	**7.If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?**	**8.Was there use of concurrent controls?**	**9.Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?**	**10.Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?**	**11.Were the assessors of exposure/risk blinded to the case or control status of participants?**	**12.Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?**	**Overall quality**
Acasuso-Díaz and Collantes-Estenvez (1998)[1]	**Reviewers' final decision**	**Yes**	**No**	**No**	**NR**	**Yes**	**Yes**	**NR**	**Yes**	**No**	**Yes**	**NR**	**No**	**5/12 Poor**
Ofluoglu et al. (2006)[26]		**Yes**	**No**	**No**	**NR**	**Yes**	**Yes**	**NA**	**NA**	**NA**	**Yes**	**Yes**	**NA**	**5/12 Poor**
Sendur, Gurer and Bozbas (2007)[5]		**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**NA**	**Yes**	**Yes**	**Yes**	**9/12 Good**
Rombaut et al., (2011)[27]		**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**NA**	**NA**	**NA**	**Yes**	**CD**	**Yes**	**7/12 Fair**
De Wandele (2014)6		**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**NA**	**NR**	**Yes**	**Yes**	**No**	**Yes**	**7/12 Fair**
Di Stefano et al., (2016)[29]		**No**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**CD**	**NA**	**7/12 Fair**
Karaaslan, Hazendaroglu and Ozturk (2000)[24]		**Yes**	**No**	**No**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**NA**	**8/12 Fair**
Lai et al., (2000)[25]		**Yes**	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**NA**	**Yes**	**Yes**	**Yes**	**NA**	**Yes**	**9/12 Good**
Molander et al., (2020)[30]		**Yes**	**Yes**	**No**	**Yes**	**CD**	**CD**	**NA**	**NA**	**NA**	**Yes**	**No**	**NA**	**4/12 Poor**

CD: cannot determine; NA: not applicable NR: not related.
Based on the overall score (0 to 12), the studies were classified as good quality and low risk of bias (≥ 9/12), fair quality and moderate risk of bias (7-8/12), or poor quality and high risk of bias (≤ 6/12).[36]

Table 5: Joanna Briggs Critical Appraisal checklist for studies reporting Quality assessment for prevalence studies exploring both hypermobility and fibromyalgia for reviewer 1, reviewer 2 and the final approved decision for the reviewers.											
Study		**1.Sample frame appropriate to target population?**	**2.Study participants sampled in an appropriate way?**	**3.Sample size adequate?**	**4.Study subjects and setting describe in detail?**	**5.Analysis conducted with sufficient coverage of the identified sample?**	**6.Valid methods to identify condition?**	**7.Condition measured in a standard reliable way?**	**8.Appropriate statistical analysis?**	**9.Response rate adequate or was low response rate managed appropriately?**	**Overall quality**
Kozangolu et al., (2015)[28]	**Reviewers' final decision**	**Unclear**	**Unclear**	**Unclear**	**No**	**No**	**Yes**	**Yes**	**Yes**	**NA**	**3/9 Moderate quality**
Bragée et al., (2020)[7]		**Yes**	**Yes**	**Unclear**	**Yes**	**Yes**	**Yes**	**Yes**	**Unclear**	**Yes**	**7/9 High quality**
Studies scoring ≥ 7/9 were considered as high quality studies with low risk of bias, studies scoring 3-6/9 were considered as moderate quality studies with moderate risk of bias, and studies scoring ≤ 2/9 were considered as low quality studies with high risk of bias.[37]											

Discussion:

The current systematic review provides a novel and comprehensive summary of the concomitant diagnosis of FMS and connective tissue disorders, reporting two clinically essential dimensions of prevalence percentage and clinical features. The concomitant diagnosis of hEDS/HSD, GJH and FMS ranged from 8.0% to 88.9%. In particular, the association prevalence of hEDS/HSD and FMS ranges from 68% to 88.9%.[28, 29] The figures were high supporting the great concomitant diagnosis of hEDS/HSD in FMS where the Brighton criteria were employed.[28, 29] In parallel, the prevalence of GJH in FMS ranges from 8.0% to 64.2%, which shows a broad range, where the Beighton criteria of an acceptable cutoff point of ≥ 4/9 was used.[1, 5, 24-26] The Beighton score is negatively correlated with age,[26] yet it seems that sample age has no impact on the reported prevalence. The youngest sample of mean age 34 years showed a low prevalence of 8%, while the oldest sample of mean age 48 years showed a prevalence of 46.6% of GJH in FMS.[5, 24] However, the highest quality studies point toward a high frequency of 46.6% and have determined that patients with FMS are more than twice as likely to have GJH than patients without FMS.[5, 25] Consequently, the findings support the hypothesis of high concomitant diagnosis of hEDS/HSD and GJH in FMS in adults. Acknowledging the potential association between hEDS/HSD, GJH and FMS should help in diagnostic accuracy, avoiding misdiagnosis and considering dual diagnosis. It is worth suspecting hEDS/HSD and GJH in people with FMS and it is worth suspecting FMS in people with hEDS/HSD and GJH for auspicious understanding, diagnosis, and management.

Both FMS and hEDS/HSD are disorders with broad spectrum ranging from mild manifestations to severe disability and their symptomatic features are overlapping.[8, 53] Such complex intersection between FMS and hEDS/HSD should be considered to correctly diagnose the patients and provide relevant management. Zimmermann (1991) and Bennet (1996) have linked the pathophysiology of pain in FMS with the clinical feature of hypermobility, explaining that joint hypermobility in FMS could increase the muscular strain and pain excitability, leading to the chronicity of pain.[17, 18] Such observation is supported by the current systematic review, which could clarify the pathophysiology of hEDS/HSD, GJH and FMS. The overlap was found to exceed the musculoskeletal system and reach other vital systems including neurological and autonomic systems as well as psychological health. Particularly, numerous symptomatic features were found significantly concomitant between hEDS/HSD, GJH and FMS. This is suggested by evidence from two good/high quality studies,[5, 7] two fair quality studies,[6,27] and only one study with poor quality.[30] Statistically significant similarities were found in pain duration, frequency of persistent pain, multidimensional pain inventory-activity, pain component of the SF-36, joint swelling, muscle weakness and neurological problems in EDS-HT and FMS.[27, 30] No statistically significant differences were noted between FMS patients with and without GJH in mean pain level, tender points count and total myalgic score.[5] Significant similarities were determined in dysautonomia and total autonomic symptoms burden between people with EDS-HT and those with FMS.[6, 27] Despite the strict selection criteria applied by De Wandele et al., (2014), where hypermobile patients were excluded from the FMS group if they fulfilled one or more of the minor criteria for EDS-HT, both groups of EDS-HT and FMS were found to have similarities in orthostatic intolerance domain, reflex syncope, vasomotor domain, gastrointestinal domain, diarrhea, and constipation and pupillomotor domains.[6] Significant similarities were also found in the psychological impact, functional impairment, and the quality of life between EDS-HT and FMS.[27, 30] No statistically significant difference was found in health status between GJH and FMS.[5] Moreover, 50% of the patients with myalgic encephalomyelitis/ chronic fatigue syndrome have GJH and 76% have FMS.[7] The conditions of hEDS/HSD, GJH and FMS are complex, and understanding their similarities in terms of symptomatic features can simplify the complexity. The large number of possible concomitant symptomatic features between hEDS/HSD, GJH and FMS and the involvement of various systems in their pathogenesis strongly suggest that management approaches need to be tailored according to the patient needs. These conditions are defined as musculoskeletal conditions; however, the involvement of other non-musculoskeletal systems should be considered during both differential diagnosis and planning individualized management.

It has been suggested that the etiology of FMS could be related to stress and vulnerability and a range of other disorders including hypothyroidism, rheumatoid arthritis and systemic lupus erythematosus were found to be highly associated with FMS.[54-55] Therefore, some of the high association between HSD/hEDS and FMS could be related to the disease burden concept. However, such cause-and-effect relationship between HSD/hEDS and FMS should be explored in future research. The old diagnostic criteria were employed by all of the reviewed studies and can broadly be considered comparable to the generalized type of HSD in the 2017 classification framework, although this cannot be assumed. It should be also acknowledged that using the old diagnostic criteria might have failed to identify the localized, peripheral, and historical HSD sub-types in the 2017 criteria as these could be diagnosed with Beighton score of 1-3/9. Future studies that use the 2017 criteria for HSD could therefore identify very different estimates of association prevalence if they include all HSD sub-types. Future work should consider reporting data on people with generalized HSD separately to facilitate comparison with historical data. This review aimed to explore the concomitant diagnosis of FMS and connective tissue disorders in adults. The results might be generalizable to people in their early thirties to mid-fifties, however the younger age group of 18 to 30 was not explored in the studies included in the review.

Numerous differences in clinical features were also suggested between hEDS/HSD, GJH and FMS, and this would provide further clarification. However, the identified differences were reported by three studies with fair/poor quality; therefore, their results should be considered with caution.[6, 27, 30] Significant increase was suggested in pain numerical rating scale, multidimensional pain inventory (pain severity, distress, interference and control) and the number of pain regions in people with FMS compared to those with EDS/HMS.[30] However, the FMS group was significantly older; mean (SD) of 43.57 (10.34) years, than the EDS/HMS group; 35.97 (10.81) years, which could explain the significant increase of complaints in FMS.[30] Patients with FMS were also found to have more headache, muscle pain and pain severity compared to EDS-HT.[27] Statistically higher fatigue and muscle stiffness, and greater sleep, cognitive, psychological, and emotional problems were found compared to EDS-HT/HMS.[6, 27, 30] Yet, patients with EDS-HT showed more symptoms of muscle cramps, tendinitis, skin problems, joint instability, increase in bladder function, and scored less in the domain of sleep dysfunction compared to FMS group.[6, 27] Notably, Rombaut et al.'s (2011) FMS group seems slightly older than the EDS-HT group; 44.3 (9.88) and 40.1 (11.94) years old respectively, and De Wandele et al., (2014) have excluded patients with hypermobility from the FMS group which could explain the differences identified.[6, 27] Despite the differences in some of the clinical features between hEDS/HSD, GJH and FMS, the interaction of the different symptoms could have essential role in complicating the pathogenesis of the conditions, especially in patients with dual diagnosis. For instance, the pathogenesis of joint pain in patients with a positive FMS diagnosis would differ than in patients with positive diagnosis of FMS and hEDS/HSD or GJH, where joint hypermobility and instability would adversely complicate the pathogenesis of joint pain in patients with FMS. Ultimately, such dual diagnosis would require different considerations for management.

Unfortunately, the clinical phenotypes of HSD/hEDS and FMS demonstrate significant overlap in terms of pain, swelling, muscle weakness, neurological problems, autonomic symptoms of orthostatic intolerance, reflex syncope, vasomotor, gastrointestinal, diarrhea, constipation and pupillomotor, in addition to functional impairment and quality of life index (Appendix II). Some phenotypes were found statistically higher in HSD/hEDS such as symptoms of joint instability, tendinitis, skin problems and bladder function; and some phenotypes were found statistically higher in FMS such as headache and sleep problems (Appendix II). However, it should be noted that the differences in phenotypes between HSD/hEDS and FMS do not mean that these phenotypes are exclusive for FMS or EDS-HT, only that their prevalence is higher in one condition compared to the other, and they can be observed in both conditions. Therefore, they should not be used as distinctive phenotypes for differential diagnosis.

To our knowledge there is no previous similar systematic review, therefore comparing the results with other literature is difficult. The review included eleven studies, however only three studies are at low risk of bias,[5, 7, 25] while five studies are at moderate risk of bias.[6, 24, 27-29] Therefore, the risk of bias should be considered. Although the review structured the results according to 1) hEDS/HSD (i.e. symptomatic) and 2) GJH (often asymptomatic), it should be noted that most of the reviewed studies explored patients with a primary diagnosis of FMS. FMS is a chronic symptomatic condition, therefore, GJH in this review is likely to reflect hypermobility in symptomatic individuals.

FMS and connective tissue disorders were found to be highly associated in terms of prevalence and symptomatic features. Therefore, clinicians should be aware of the potential overlap between FMS and hEDS/HSD and GJH. The diagnosis of these conditions relies on widespread pain, however, considering tender points in the examination could lead to the diagnosis of FMS, and considering joint hypermobility in the examination could lead to the diagnosis of hEDS/HSD. It is unknown if clinicians' background, experience and knowledge would have an impact on the diagnosis given. As has been debated worldwide, hypermobility syndrome is often overlooked and underrecognized, leading to late diagnosis. The results of the current systematic review support considering the diagnosis of hEDS/HSD and GJH in people with FMS (and vice versa). Future research is needed to examine the impact of the clinicians' background and knowledge of connective tissue disorders on their diagnostic decisions. It is highly recommended to closely consider screening for both conditions. Clinicians can then decide on a case-by-case basis which are the predominant features and work with patients to help them manage their symptoms.

Contributors: NA. study idea, design, first reviewer, critical appraisal, data analysis, writing the manuscript and approving the final draft. MA. The third reviewer, critical appraisal, and approving the final draft. TA. The second reviewer, critical appraisal, and approving the final draft. S.P. study idea, data analysis, critically reviewing the manuscript, and approving the final draft.

Declaration of interests: We declare no competing interests.

Data sharing: Data are available upon request.

Acknowledgments: None.

Ethical approval: Non applicable.

Funding: None.

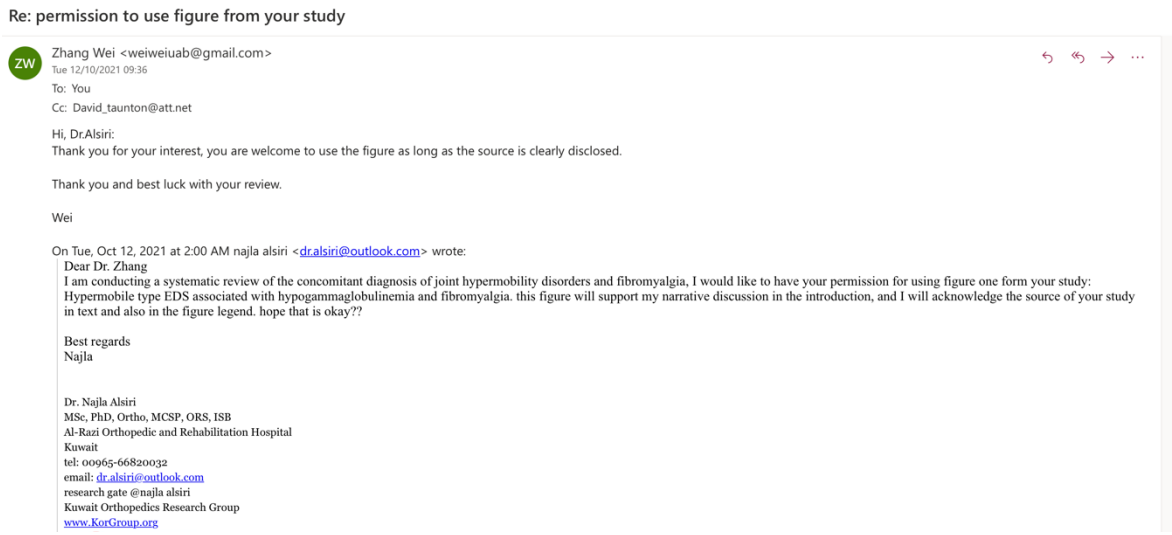
References:

1. Acasuso-Díaz M, Collantes-Estévez E. Joint hypermobility in patients with fibromyalgia syndrome. *Arthritis Care Res*. 1998; **11** (1): 39-42.
2. Sahin N, Atik A, Dogan E. Clinical and demographic characteristics and functional status of the patients with fibromyalgia syndrome. *North Clin Istanb*. 2014; **1** (2): 89-94. doi: 10.
3. Assumpção, A., Cavalcante, A.B., Capela, C.E. *et al.* Prevalence of fibromyalgia in a low socioeconomic status population. *BMC Musculoskelet Disord* **10**, 64 (2009).
4. Marques A, Santo A, Berssaneti A, Matsutani L, Yuan S., Prevalence of fibromyalgia: literature review update, Revista Brasileira de Reumatologia (English Edition) 2017; 57(4): 356-363. https://doi.org/10.1016/j.rbre.2017.01.005.
5. Sendur OF, Gurer G, Bozbas GT. The frequency of hypermobility and its relationship with clinical findings of fibromyalgia patients. *Clin Rheumatol*. 2007; **26** (4): 485-7.
6. De Wandele I, Calders P, Peersman W, Rimbaut S, De Backer T, Malfait F, De Paepe A, Rombaut L. Autonomic symptom burden in the hypermobility type of Ehlers-Danlos syndrome: a comparative study with two other EDS types, fibromyalgia, and healthy controls. *Semin Arthritis Rheum*. 2014; **44** (3): 353-61.
7. Bragée B, Michos A, Drum B, Fahlgren M, Szulkin R, Bertilson BC. Signs of Intracranial Hypertension, Hypermobility, and Craniocervical Obstructions in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. *Front Neurol*. 2020; **11**: 828. doi: 10.3389%2Ffneur.2020.00828
8. Castori M, Tinkle B, Levy H, Grahame R, Malfait F, Hakim A. A framework for the classification of joint hypermobility and related conditions. *Am J Med Genet C Semin Med Genet*. 2017; **175** (1): 148-157.
9. Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, Bloom L, Bowen JM, Brady AF, Burrows NP, Castori M, Cohen H, Colombi M, Demirdas S, De Backer J, De Paepe A, Fournel-Gigleux S, Frank M, Ghali N, Giunta C, Grahame R, Hakim A, Jeunemaitre X, Johnson D, Juul-Kristensen B, Kapferer-Seebacher I, Kazkaz H, Kosho T, Lavallee ME, Levy H, Mendoza-Londono R, Pepin M, Pope FM, Reinstein E, Robert L, Rohrbach M, Sanders L, Sobey GJ, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Wheeldon N, Zschocke J, Tinkle B. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet C Semin Med Genet*. 2017; **175** (1): 8-26.
10. Clark CJ, Simmonds JV. An exploration of the prevalence of hypermobility and joint hypermobility syndrome in Omani women attending a hospital physiotherapy service. *Musculoskeletal Care*. 2011; **9** (1): 1-10.
11. Connelly, E, Hakim A, Davenport, A, Simmonds, J. A Study Exploring the Prevalence of Joint Hypermobility Syndrome in Patients Attending a Musculoskeletal Triage Clinic. *Physiotherapy Practice and Research*. 2015; **36** (1): 43 – 53.
12. Carbonell-Bobadilla N, Rodríguez-Álvarez AA, Rojas-García G, Barragán-Garfias JA, Orrantia-Vertiz M, Rodríguez-Romo R. Síndrome de hipermovilidad articular [Joint hypermobility syndrome]. *Acta Ortop Mex*. 2020; **34** (6): 441-449.
13. Malhotra A, Pace A, Ruiz Maya T, Colman R, Gelb BD, Mehta L, Kontorovich AR. Headaches in hypermobility syndromes: A pain in the neck? *Am J Med Genet A*. 2020; **82** (12): 2902-2908.
14. Simmonds JV. Advances in assessment of hypermobility-related disorders. *Am J Med Genet C Semin Med Genet*. 2021; **187** (4): 453-457.
15. Bartels EM, Danneskiold-Samsøe B. Histological abnormalities in muscle from patients with certain types of fibrositis. *Lancet*. 1986; **5** ;1(8484):755-7.
16. Goldman JA. Hypermobility and deconditioning: important links to fibromyalgia/fibrositis. *South Med J*. 1991; **84** (10): 1192-6.
17. Zimmermann M. Pathophysiological mechanisms of fibromyalgia. *Clin J Pain*. 1991; **7** Supp 1: 8-15.
18. Bennet RM. Fibromyalgia and the disability dilemma: a new era in understanding a complex, multidimensional pain syndrome. *Arthritis Rheum.* 1996; **39** :1627-34.
19. Zhang W, Windsor K, Jones R, Taunton DO. Hypermobile type Ehlers-Danlos syndrome associated with hypogammaglobulinemia and fibromyalgia: A case-based review on new classification, diagnosis, and multidisciplinary management. *Clin Case Rep*. 2019; **19** ;7 (4): 680-685.
20. Larsson LG, Mudholkar GS, Baum J, Srivastava DK. Benefits and liabilities of hypermobility in the back pain disorders of industrial workers. *J Intern Med*. 1995; **238** (5): 461-7.
21. Simmonds JV, Keer RJ. Hypermobility and the hypermobility syndrome. *Man Ther*. 2007; **12** (4): 298-309.

22. Scheper MC, Juul-Kristensen B, Rombaut L, Rameckers EA, Verbunt J, Engelbert RH. Disability in Adolescents and Adults Diagnosed With Hypermobility-Related Disorders: A Meta-Analysis. *Arch Phys Med Rehabil*. 2016; **97** (12): 2174-2187.
23. Kumar A, Wadhwa S, Acharya P, Seth S, Khokhar S, Singh RV, Bali K, Rawall S, Singhania S, Singh N. Benign joint hypermobility syndrome: a hospital-based study from northern India, *Indian Journal of Rheumatology*. 2006; **1** (1): 8-12.
24. Karaaslan Y, Haznedaroglu S, Oztürk M. Joint hypermobility and primary fibromyalgia: a clinical enigma. *J Rheumatol*. 2000; **27** (7):1774-6.
25. Lai S, Goldman JA, Child AH, Engel A, Lamm SH. Fibromyalgia, hypermobility, and breast implants. *J Rheumatol.* 2000; **27** (9): 2237-41.
26. Ofluoglu D, Gunduz OH, Kul-Panza E, Guven Z. Hypermobility in women with fibromyalgia syndrome. *Clin Rheumatol*. 2006; **25** (3): 291-3.
27. Rombaut L, Malfait F, De Paepe A, Rimbaut S, Verbruggen G, De Wandele I, Calders P. Impairment and impact of pain in female patients with Ehlers-Danlos syndrome: a comparative study with fibromyalgia and rheumatoid arthritis. *Arthritis Rheum*. 2011; **63** (7):1979-87.
28. Kozanoglu E, Coskun Benlidayi I, Eker Akilli R, Tasal A. Is there any link between joint hypermobility and mitral valve prolapse in patients with fibromyalgia syndrome? *Clin Rheumatol*. 2016; **35** (4): 1041-4.
29. Di Stefano G, Celletti C, Baron R, Castori M, Di Franco M, La Cesa S, Leone C, Pepe A, Cruccu G, Truini A, Camerota F. Central sensitization as the mechanism underlying pain in joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type. *Eur J Pain*. 2016; **20** (8): 1319-25.
30. Molander P, Novo M, Hållstam A, Löfgren M, Stålnacke BM, Gerdle B. Ehlers-Danlos Syndrome and Hypermobility Syndrome Compared with Other Common Chronic Pain Diagnoses-A Study from the Swedish Quality Registry for Pain Rehabilitation. *J Clin Med.* 2020; **9** (7): 2143.
31. Linares-Espinós E, Hernández V, Domínguez-Escrig JL, Fernández-Pello S, Hevia V, Mayor J, Padilla-Fernández B, Ribal MJ. Methodology of a systematic review. *Actas Urol Esp (Engl Ed).* 2018; **42** (8): 499-506.
32. Page M J, McKenzie J E, Bossuyt P M, Boutron I, Hoffmann T C, Mulrow C D et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021; **372** (71): doi:10.1136/bmj.n71.
33. Beighton, P., De Paepe, A., Steinmann, B., Tsipouras, P. and Wenstrup, R. (1998) Ehlers-Danlos syndrome: revised nosology, Villefracnche, 1997. *American Journal of Medical Genetics.* 77, pp. 31-37.
34. Beighton, P., Solomon, L. and Soskolne, C. (1973) Articular mobility in an African population. *Annals of the Rheumatic Diseases*. 32, pp. 413-418.
35. Wolfe F, Clauw DJ, Fitzcharles M-A, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res*. 2010;62(5):600-610.
36. National Institutes of Health (2014). Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort
37. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. *Int J Evid Based Healthc*. 2015; **13** (3):147-53.
38. Tavakkol R, Kavi E, Hassanipour S, Rabiei H, and Malakoutikhah M. The global prevalence of musculoskeletal disorders among operating room personnel: A systematic review and meta-analysis. *Clinical Epidemiology and Global Health*. 2020; 8 (4): 1053-1061.
39. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas.* 1960; **20** :37–46.
40. McHugh ML. Interrater reliability: the kappa statistic. *Biochemia medica.* 2012; **22** (3): 276–282.
41. Hoppmann RA, Reid RR. Musculoskeletal problems of musicians: a niche for the rheumatologist. *J Clin Rheumatol*. 1995; **1** (1): 23-5.
42. Klemp P. Hypermobility. *Ann Rheum Dis.* 1997; **56** (10): 573-5.
43. Hudson N, Fitzcharles MA, Cohen M, Starr MR, Esdaile JM. The association of soft-tissue rheumatism and hypermobility. *Br J Rheumatol.* 1998; **37** (4): 382-6.
44. Fitzcharles MA. Is hypermobility a factor in fibromyalgia? *J Rheumatol*. 2000; **27** (7): 1587-9.
45. Holman AJ. Is hypermobility a factor in fibromyalgia? *J Rheumatol.* 2002; **29** (2): 396-8.
46. Bennett R. Myofascial pain syndromes and their evaluation. *Best Pract Res Clin Rheumatol*. 2007; **21** (3): 427-45.
47. Eyigor S, Ozdedeli S, Durmaz B. The prevalence of generalized soft tissue rheumatic conditions in Turkish medical students. *J Clin Rheumatol.* 2008; **14** (2): 65-8.

48. Bravo JF. Síndrome de Ehlers-Danlos con especial énfasis en el síndrome de hiperlaxitud articular [Ehlers-Danlos syndrome, with special emphasis in the joint hypermobility syndrome]. *Rev Med Chil*. 2009; **137** (11): 1488-97.
49. Kovacic K, Chelimsky TC, Sood MR, Simpson P, Nugent M, Chelimsky G. Joint hypermobility: a common association with complex functional gastrointestinal disorders. *J Pediatr.* 2014; **165** (5): 973-8.
50. Fikree A, Aktar R, Grahame R, Hakim AJ, Morris JK, Knowles CH, Aziz Q. Functional gastrointestinal disorders are associated with the joint hypermobility syndrome in secondary care: a case-control study. *Neurogastroenterol Motil*. 2015; **27** (4): 569-79.
51. Cutsforth-Gregory JK, Sandroni P. Clinical neurophysiology of postural tachycardia syndrome. *Handb Clin Neurol*. 2019; **161**: 429-445.
52. Eccles JA, Thompson B, Themelis K, Amato ML, Stocks R, Pound A, Jones AM, Cipinova Z, Shah-Goodwin L, Timeyin J, Thompson CR, Batty T, Harrison NA, Critchley HD, Davies KA. Beyond bones: The relevance of variants of connective tissue (hypermobility) to fibromyalgia, ME/CFS and controversies surrounding diagnostic classification: an observational study. *Clin Med (Lond).* 2021; **21** (1): 53-58.
53. Understanding fibromyalgia and its related disorders. Prim Care Companion J Clin Psychiatry. 2008;10(2):133-44. doi: 10.4088/pcc.v10n0208. PMID: 18458727; PMCID: PMC2292439.
54. Furness PJ, Vogt K, Ashe S, Taylor S, Haywood-Small S, Lawson K. What causes fibromyalgia? An online survey of patient perspectives. Health Psychol Open. 2018 Sep 25;5(2):2055102918802683. doi: 10.1177/2055102918802683. PMID: 30275965; PMCID: PMC6158621.
55. Weir PT, Harlan GA, and Nkoy FL. et al. The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th Revision codes. *J Clin Rheumatol*. 2006 12:124–128.

Appendix 1
Figure 1 adaptation permission



Re: permission to use figure from your study

Zhang Wei <weiweiuab@gmail.com>
Tue 12/10/2021 09:36

To: You
Cc: David_taunton@att.net

Hi, Dr.Alsiri:
Thank you for your interest, you are welcome to use the figure as long as the source is clearly disclosed.

Thank you and best luck with your review.

Wei

On Tue, Oct 12, 2021 at 2:00 AM najla alsiri <dr.alsiri@outlook.com> wrote:

Dear Dr. Zhang
I am conducting a systematic review of the concomitant diagnosis of joint hypermobility disorders and fibromyalgia, I would like to have your permission for using figure one form your study: Hypermobile type EDS associated with hypogammaglobulinemia and fibromyalgia. this figure will support my narrative discussion in the introduction, and I will acknowledge the source of your study in text and also in the figure legend. hope that is okay??

Best regards
Najla

Dr. Najla Alsiri
MSc, PhD, Ortho, MCSP, ORS, ISB
Al-Razi Orthopedic and Rehabilitation Hospital
Kuwait
tel: 00965-66820032
email: dr.alsiri@outlook.com
research gate @najla alsiri
Kuwait Orthopedics Research Group
www.KorGroup.org

Appendix II

Appendix II: Summary of clinical profiles of phenotypes between HSD/EDS-HT and FMS			
Phenotype	**Similarities**	**Differences**	**Evidence certainty**
Pain	Joint pain	Headache ⇑ FMS Muscle pain ⇑ FMS Pain severity ⇑ FMS	Fair [27]
	Pain duration Multidimensional pain inventory Persistent pain SF-36 pain component score	Numerical rating scale ⇑ FMS Multidimensional pain inventory ⇑ FMS Pain severity ⇑ FMS Number of painful regions ⇑ FMS Multidimensional pain inventory-control subscale ⇑ EDS-HT	Poor [30]
Joint instability	Not identified	Symptoms of joint instability ⇑ EDS-HT (joint dislocation and distortions, pelvis instability and snapping and joint locking)	Fair [27]
Autonomic symptoms	Dysautonomia Total autonomic symptoms burden: orthostatic intolerance, reflex syncope, vasomotor, gastrointestinal, diarrhea and constipation and pupillomotor	Bladder function ⇑ EDS-HT	Fair [6, 27]
Mitral valve prolapse	Mitral valve prolapse significantly increased in patients with FMS when they meet the diagnosis of JHS		Moderate [28]
Myalgic encephalomyelitis/ chronic fatigue syndrome	50% of the patients with myalgic encephalomyelitis/ chronic fatigue syndrome were found to have GJH, 20% were found to have hEDS, and 76% were found to have FMS		High [7]
Other symptoms	Swelling Muscle weakness Neurological problems Functional impairment measured with the Sickness impact profile	Fatigue ⇑ FMS Muscle stiffness ⇑ FMS Higher muscle cramps ⇑ EDS-HT Tendinitis ⇑ EDS-HT Skin problems ⇑ EDS-HT	Fair [27]
Psychological health	Psychological impact		Good [5]
		Cognitive and emotional problems ⇑ FMS Psychological impairment in daily life ⇑ FMS	Fair [27]
		Hospital Anxiety and Depression Scale ⇑ FMS the SF-36-mental component score ⇑ FMS	Poor [30]
Sleep disturbance	Not identified	Problems in sleep ⇑ FMS Sleep dysfunction ⇑ FMS	Fair [6, 27]
Quality of life	European Quality of Life Index		Poor [30]