KACPERCZYK, Julia, CZYŻ, Witold, WÓJCIKIEWICZ, Michalina, ARCZEWSKI, Filip, DZIEDZIC, Karol, KULBACKA, Julia, WOJSZCZYK, Maciej, ZYS, Damian, PASEK, Piotr and RYNIECKA, Julia. Does it take the joints to stretch a mind? The ADHD and General Joint Hypermobility connection. Quality in Sport. 2025;37:57296. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.37.57296
https://apcz.umk.pl/QS/article/view/57296

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.

Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).

Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego iNauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.

Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 24.12.2024. Revised: 17.01.2025. Accepted: 17.01.2025 Published: 20.01.2025.

Does it take the joints to stretch a mind? The ADHD and General Joint Hypermobility connection

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity-impulsivity, or both, which negatively affect the quality of life for children and adults worldwide. ADHD is known to cause significant psychosocial distress, including academic failure, divorce, unemployment, and incarceration, and increases the risk of developing psychiatric disorders such as depression, anxiety, and substance abuse.

While its cognitive and psychological impacts are yet well-documented, the implications of ADHD for physical health have only recently begun to receive increasing attention. Some of the known non-psychiatric health challenges associated with ADHD include obesity, autonomic dysregulation, musculoskeletal symptoms and joint hypermobility.

This paper investigates recently discovered links between ADHD and symptoms of joint hypermobility, and focuses on the prevalence of generalized joint hypermobility, as well as ADHD comorbidity in connective tissue-related conditions, such as Ehlers-Danlos syndrome and hypermobility spectrum disorder.

Aim

This study aims to:

1. Provide a comprehensive review of recently published literature explaining attention-deficit/ hyperactivity disorder (ADHD) co-occurrence with joint hypermobility-related conditions.
2. Contribute to a better understanding of the complex nature of joint hypermobility and the hEDS-ADHD association.
3. Explore the biological and psychosocial mechanisms underlying these associations and their clinical implications.

Keywords: “ADHD” , “attention defficit hyperactivity disorder”, “joint hypermobility”, “hypermobile Ehlers-Danlos syndrome”

List of abbreviations

ADHD - attention-deficit/hyperactivity disorder

ASD - autism spectrum disorder

EDS - Ehlers-Danlos syndrome

hEDS - hypermobile Ehlers-Danlos syndrome

HSD - hypermobile spectrum disorder

JH -joint hypermobility

GJH - generalized joint hypermobility

CNS - central nervous system

ANS - autonomic nervous system

POTS - postural orthostatic tachycardia syndrome

NEP - neuroconnective endophenotype

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by abnormal problems with attention maintenance (inattentive presentation), hyperactivity-impulsivity (hyperactive presentation), emotional dysregulation, and executive function deficits[1, 2], causing significant disturbances in psychological, social and emotional health of the individual. It is commonly diagnosed with prevalence of 5-9.8% in the pediatric population, and 2,5%-4.4% in adults [2,3].

Several studies point out that ADHD diagnosis frequently appears to co-occur with other psychological disorders, predominantly autistic spectrum disorder (ASD),found in 38.5-40.2% of ADHD patients [4, 5], followed by anxiety disorders, personality and affective disorders[4, 6].

Despite the growing understanding of the psychiatric difficulties related to neurodiversity, the physical health outcomes of ADHD have just currently gained more attention.

This systematic review is aimed to further explore the trend, connecting the hypermobility-related disorders and ADHD/ASD, and to collect the existing evidence on associations between joint hypermobility, dysautonomia, and neurodiversity in hEDS individuals.

Methods

A comprehensive literature search using the PubMed and Google Scholar databases has been performed. This paper presents a systematic review of peer-reviewed articles from 2015 to 2024, focusing on the connection between ADHD and joint hypermobility. Keywords included "ADHD", “generalized joint hypermobility", “Ehlers-Danlos syndrome"," and “hypermobile Ehlers-Danlos Syndrome.” Study selection was based on their relevance to diagnostic implications, and their contribution to better understanding of ADHD and hEDS etiology.

Study selection focused on case studies and systematic reviews published since 2015, consisting of reliable data on the correlation between hEDS/HSD and ADHD/ASD. Particular emphasis was

placed on studies exploring shared biological mechanisms, developmental trajectories, and clinical implications.

Results

The latest debate on the joint hypermobility-related disorders and the Ehlers-Danlos syndrome, focused on their heterogeneity, provided significant insights into the definitions and understanding of GJH, HSD, and hEDS.

Since the introduction of the 2017 EDS criteria[7], the genetic basis and shared comorbidities of the 13 recognized EDS subtypes have been comprehensively characterized (Malfait et al., 2017).

However, hypermobile EDS (hEDS) remains the only subtype for which a defined genetic basis has yet to be identified, highlighting a significant gap in current understanding.[7]

An increased prevalence of systemic comorbidities in hEDS and HSD have been highlighted, as the psychological conditions, including neurodevelopmental disorders, have been well-documented among individuals with hEDS/HSD.[8, 9, 10, 11]

1. Generalized Joint Hypermobility: definitions and diagnostic criteria

Joint hypermobility (JH) defines a state of joint laxity, and an extended range of motion of a joint or group of joints, along their physiological axes. [12, 13]

Generalized joint hypermobility (GJH) describes a presentation of JH in multiple joints and is found in 2-57% of the general population.[12, 13, 14] Prevalence differences could be explained by age, gender, ethnicity, and activity of the population.[13] GJH can be asymptomatic or symptomatic, the latter being found in 10% of GJH individuals, and accompanied by musculoskeletal issues, pain, or dysautonomia. [13, 15]. Symptomatic GJH has been identified as major criteria for diagnosis of either hypermobile type of Ehlers-Danlos Syndrome (hEDS), or Hypermobility Spectrum Disorders (HSD) [7, 12, 13, 14].

This review defines GJH using the Beighton Score (BS) cutoff of 4 and above [7, 12], and considers age-specific thresholds established in the 2017 hEDS diagnostic criteria[7]. Beighton score was considered positive with ≥5 points in adults up to the age of 50, and ≥4 points in those over the age of 50.

2. Neurodevelopmental Associations of GJH

As summarized in Table 1, several studies have demonstrated a significant association between ADHD and GJH. Although earlier hints of the connection between joint hypermobility spectrum and neurodevelopmental disorders existed, it is the last 15 years that this relationship has been

documented more thorougly. One early research (Dogan et al. 2011) reported generalized hypermobility in 32% of 54 patients with ADHD, compared to 14% of control[16], while another (Shiari et al. 2013) reported the prevalence of GJH to be 74% in 86 children with ADHD, compared to 13% of controls[17]. The connection between GJH and ADHD was further substantiated by Glans et al. (2021), which found significantly increased prevalence of GJH in the ADHD group (OR of 4.7). Moreover, when symptomatic GJH was considered, the correlation became even stronger (OR of 6.9) [18].

In a matched nationwide population-based cohort study (Cederlöf et al., 2016) the connection was further solidified, demonstrating a significant increase in ADHD prevalence among individuals with hEDS or GJH, comparing to their non-EDS siblings. [19]

Additionally, the age-related variation of ADHD prevalence in hEDS children has been discovered (Kindgren et al. 2021), where comorbities increased from 16% in younger children, with additional 7% under evaluation, to 46% in adolescents of 17-18 years. [20]

These findings solidify a need for further research focusing on potential diagnostic implications, as they seem to confirm that patients presenting with neurodevelopmental disorders like ADHD should be considered for connective tissue disorders evaluation, particularly if they exhibit unexplained somatic symptoms. [8, 11, 21, 22, 23]

Table 1. Summary of studies investigating the ADHD-GJH association

Reference	Cohort Description	ADHD Prevalence	GJH Prevalence	Odds Ratio (OR)
Dogan et al. (2011)	54 ADHD patients, 22 controls	N/A	32% in ADHD, 14% controls	N/A
Shiari et al. (2013)	86 ADHD children, 13 controls	N/A	74% in ADHD, 13% controls	N/A
Cederlöf et al. (2016)	EDS cohort vs general population	N/A	N/A	6.02 (95% CI: 3.96-9.15)
Glans et al. (2021)	431 ADHD adults, 417 controls	N/A	N/A	4.7 (GJH), 6.9 (symptomatic GJH)
Kindgren et al. (2021)	Children with HSD/ hEDS	16% ADHD, 7% under evaluation	N/A	N/A

Table 1. provides an overview of studies exploring the prevalence of joint hypermobility (JH) and generalized joint hypermobility (GJH) in individuals with attention-deficit/hyperactivity disorder (ADHD). It includes cohort descriptions, ADHD prevalence rates, GJH prevalence rates, and reported odds ratios (ORs) where applicable.

Discussion

This systematic review highlights a compelling link between generalized joint hypermobility (GJH), hypermobile Ehlers-Danlos syndrome (hEDS), and attention-deficit/hyperactivity disorder (ADHD). The emerging concept of a neuroconnective endophenotype suggests a shared biological and clinical foundation underlying these conditions, which warrants further investigation. [21, 24, 25]

1. MECHANISMS OF INTERACTION AND OVERLAP

The proposed mechanisms linking hEDS and ADHD encompass structural, functional, and systemic factors. Table 2 outlines the suggested underlying mechanisms of the ADHD and hypermobility-related disorders connection, highlighting shared pathways.

Impaired collagen synthesis is likely a cornerstone mechanism linking hEDS to ADHD. [22, 23, 26, 27, 28, 29] Collagen is a primary structural component of connective tissues throughout the body, also presenting in the central nervous system (CNS). These abnormalities may disrupt the integrity of the brain, such as the corpus callosum, crucial for communication between the hemispheres.

These structural changes can lead to compromised neural connectivity and white matter integrity, which are essential for attentional control and cognitive processing. [25, 28, 29, 30] The resultant deficits in executive functioning and motor coordination are reminiscent of ADHD symptoms, including inattention, impulsivity, and motor restlessness [22, 29, 30].

Table 2. Potential Mechanisms underlying the connection between GJH/hEDS and ADHD

Suggested mechanism	Description	Key References
Neuroconnective Endophenotype	A concept of a unifying phenotype of connective tissue and neurodevelopmental disorders characterized by joint hypermobility, autonomic dysfunction, and neurodevelopmental symptoms	21, 23, 24
Central Nervous System Impact	Connective tissue abnormalities may affect brain structures, including white matter, impacting neurodevelopment and executive functions associated with ADHD.	21, 22, 23, 25, 27, 29
Autonomic Nervous System Dysregulation	Autonomic dysfunction (e.g., POTS) seen in hEDS/HSD may amplify ADHD-like symptoms, predominantly inattention, hyperactivity and anxiety.	10, 23, 25, 26, 31, 33
Pain and Sensory Dysregulation	Chronic pain and sensory hypersensitivity in hEDS/HSD may alter attention regulation, contributing to ADHD-like features	20, 21, 22, 31
Dopaminergic Pathways	Potential overlap in dopaminergic dysfunction between ADHD and hEDS, affecting motor control, attention, and impulsivity.	7, 22, 26, 27, 30

Fatigue and Sleep Dysregulation	Sleep issues (common in hEDS/HSD) are associated with cognitive difficulties and ADHD-like traits. Sleep disturbances are known to be more prevalent in ADHD individuals.	2, 8, 23
Stress and Anxiety Amplification	Increased prevalence of anxiety disorders in hEDS may exacerbate ADHD symptoms via heightened stress responses.	23, 27, 28, 29, 30

Table 2. summarizes the clinical manifestations, potential underlying mechanisms, and shared symptomatology observed in hypermobile Ehlers-Danlos syndrome (hEDS), hypermobility spectrum disorders (HSD), attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder (ASD). The overlap highlights the interplay of connective tissue anomalies, autonomic dysfunction, pain sensitivity, fatigue, psychological comorbidity, and motor challenges.

Collagen abnormalities lead to proprioceptive feedback alteration, which is observed in hEDS individuals. [31] Disrupted proprioception affects sensory processing pathways, which are essential for integrating internal bodily signals and maintaining a stable sense of self. [18, 23, 28, 32] This can manifest as motor dyscoordination and body awareness impairment, core features of ADHD. [1, 8, 9, 11] Thus, proprioceptive dysregulation in hEDS contributes to the sensory sensitivity and motor dysfunction observed in ADHD, further linking these conditions. [27, 28, 31, 32]

Dysregulation of the Autonomic Nervous System (ANS) with conditions such as Postural Orthostatic Tachycardia Syndrome (POTS), characterized by excessive heart rate increases upon standing, is observed in approximately 40-50% of individuals with hEDS and may be prevalent among ADHD patients experiencing autonomic instability. [10, 25, 26, 33] These autonomic dysfunctions could amplify ADHD symptoms, including inattention, hyperactivity, and anxiety [10, 22, 23, 25, 28, 30]. ANS instability may exacerbate stress responses, cognitive fog, and fatigue, suggesting a bidirectional influence between autonomic and neurodevelopmental challenges.[25, 27, 28, 30].

Heightened pain sensitivity and sensory hypersensitivity, common in hEDS [32], may impair cognitive processes, emotional regulation, and increase distractibility. [25, 27, 30] Chronic pain not only affects the sensory processing but also impacts executive functioning and mood regulation, which are pivotal in ADHD [22, 25, 27, 32, 34, 35]. This interplay suggests that chronic pain and sensory dysregulation may act as mediators linking hEDS and ADHD, with hEDS potentially serving as a contributory factor to the severity and management of ADHD symptoms. [22, 23, 24, 27, 32, 34].

These shared pathophysiological features of impaired collagen synthesis, dysregulated proprioception, and chronic pain, appear to affect both physical and cognitive functions, and may underlie the co-occurrence of motor coordination challenges and attentional deficits in individuals

with hEDS and ADHD [1, 6, 22, 26, 27]. Notably, autonomic dysfunction, such as POTS, exacerbates symptoms like fatigue, brain fog, and inattention, which overlap with ADHD presentations [10, 25, 26, 33, 34]. Other interesting factors considered to participare in hEDS-ADHD association, are immune and endocrine dysregulation [36]. Hormonal sensitivity during puberty, menstruation, and postpartum periods has been identified a as potential factor exacerbating hEDS symptoms, potentially increasing the primary challenges faced by neurodiverse individuals and causing disturbances in neurodevelopment [36].

The role of dopaminergic dysfunction further elucidates the overlap between these conditions, as they are crucial for motor control, attention, and impulsivity, and disruptions within these pathways are commonly implicated in ADHD. [7, 29] Similarly, dopaminergic imbalances in hEDS may underpin motor deficits, cognitive challenges, and emotional dysregulation, contributing to both conditions' symptomatology [27, 30]. Disruptions in dopaminergic signaling could explain the shared neurobiological pathways linking hEDS and ADHD, including difficulties with executive functioning, impulsivity, and attention [10, 23, 24, 25, 28, 29, 30].

The concept of a neuroconnective endophenotype (NEP), introduced by Bulbena et al. (2023), provides a unifying framework for understanding these connections. NEP characterizes the co-occurrence of joint hypermobility, autonomic dysfunction, and neurodevelopmental atypisms such as ADHD [21, 24]. This model posits a linkage between systemic physiological traits and cognitive and behavioral manifestations, providing a better understanding of the shared genetic and biological pathways influencing both connective tissue integrity and neural development. The integration of systemic physiological factors with neural developmental processes presents a more holistic view of the pathophysiology underlying these conditions. [21, 24]

2. Clinical implications

Investigating the research field, shared symptomatology comes into the picture. Most prevalent systemic complaints common between hEDS and ADHD include chronic pain and fatigue, orthostatic intolerance and autonomic dysregulation, while psychiatric complaints are predominantly sleep disturbances, anxiety, and emotional dysregulation. [29, 32, 37, 38, 39] Clinical presentation in affected individuals, and possible mechanisms leading to the development

of reported symptoms and similar features are presented in Table 3.

Table 3. Distinct Mechanisms of Shared Clinical Manifestations and Symptomatology in hEDS/HSD and ADHD/ASD

Clinical manifestation	Possible underlying sequence		Shared Symptomatology
	hEDS/HSD	ADHD/ASD	
Connective tissue anomalies	Impaired collagen synthesis; altered proprioception; joint instability [22, 25]	Potential impact of atypical neurodevelopment; motor and sensory challenges [29]	Chronic pain, clumsiness, motor coordination difficulties, proprioceptive impairments
Autonomic nervous system dysfunction	Dysautonomia (e.g., POTS, orthostatic intolerance); impaired vascular responses [37, 38]	Cognitive impairments (brain fog, inattention); mood dysregulation [9, 27, 34]	Fatigue, dizziness, inattention, exacerbated by shared autonomic instability
Pain sensitivity	Chronic pain, hyperalgesia [15, 32]	Pain-related behavioral challenges; sensitivity to discomfort [34, 38]	Amplified pain response may impact mood, behavior, and functional capacity
Fatigue	Common result of autonomic dysfunction and pain [32]	Caused by executive dysfunction, attentional difficulties and burnout [38]	Worsened by overlapping conditions, affecting both physical endurance and cognitive focus
Psychological comorbidity	Anxiety, depression; impact of chronic symptoms on mental health [8]	Increased prevalence of mood disorders, anxiety, and depression [2, 6]	Psychosocial impact, additional everyday-life alterations
Motor challenges	Motor delays, impaired sensory processing, proprioceptive difficulties [32]	Co-occurring motor and sensory processing difficulties [29]	Overlapping characteristics of physical, cognitive, and behavioral disturbances

Table 3. highlights the clinical manifestations shared between hypermobile Ehlers-Danlos syndrome (hEDS)/ hypermobility spectrum disorders (HSD) and neurodevelopmental disorders such as ADHD and ASD. It outlines the possible underlying sequences contributing to these manifestations in each condition and identifies overlapping symptomatology, emphasizing areas of potential mechanistic convergence or divergence. References are cited according to their order in the text and appear in the reference list.

Table 3. provides a detailed comparison of clinical manifestations, underlying mechanisms, and shared symptomatology between hEDS/HSD and ADHD/ASD. It identifies six key areas of overlap: connective tissue anomalies, autonomic nervous system dysfunction, pain sensitivity, fatigue, psychological comorbidity, and motor challenges. Connective tissue anomalies in hEDS/HSD, such as impaired collagen synthesis and altered proprioception, are linked to neurodevelopmental impacts and motor and sensory challenges seen in ADHD/ASD, manifesting as chronic pain and motor coordination difficulties [33, 34, 40] Dysautonomia and impaired vascular responses in hEDS/HSD, corresponds with cognitive impairments, brain fog, and mood

dysregulation manifesting in ADHD/ASD, collectively exacerbating symptoms like fatigue and inattention. [9, 10, 33, 34]

Pain sensitivity, a hallmark of chronic hyperalgesia in hEDS/HSD, overlaps with pain-related behavioral challenges in neurodevelopmental disorders, amplifying pain responses and impacting mood, behavior, and functional capacity. [27, 34, 35] Fatigue, a frequent symptom driven by autonomic dysfunction and chronic pain in hEDS/HSD, is similarly observed in ADHD/ASD where it is linked to executive dysfunction and attentional deficits [35, 41]; however, it remains unclear whether these symptoms share the same underlying mechanisms or arise independently [38]. Psychological comorbidities, such as anxiety and depression, are prevalent in both conditions, with chronic symptoms contributing to psychosocial impacts and everyday-life disruptions. [38, 39, 40]

Lastly, motor delays and proprioceptive difficulties seen in hEDS/HSD co-occur with motor and sensory processing challenges in ADHD/ASD, leading to overlapping physical, cognitive, and behavioral disturbances. [28, 41]

While these shared symptoms suggest potential pathophysiological connections, it is not yet fully understood whether they stem from common mechanisms or represent distinct processes contributing to similar outcomes. [38] This comparison underscores the systemic and neurodevelopmental interplay between these conditions, emphasizing the need for interdisciplinary evaluation and further research to clarify the underlying mechanisms. Early identification of co-occurring ADHD and GJH/hEDS/HDS symptoms can facilitate timely, interdisciplinary management strategies that improve patient outcomes. [22, 27] Clinicians are encouraged to screen ADHD patients for joint hypermobility and assess for autonomic dysfunction when unexplained somatic symptoms, such as fatigue, dizziness, or chronic pain, are present. [21, 23] A comprehensive evaluation and understanding of the shared symptomatology between ADHD and hEDS, including chronic pain, fatigue, anxiety, and sleep disturbances, can inform the development of tailored interventions. [23, 27]

3. Limitations and Future Directions

While progress has been made in identifying associations, causative factors remain speculative. Many studies are constrained by small sample sizes and heterogeneous methodologies, limiting the generalizability of findings. Future research should focus on longitudinal studies to elucidate the causal relationships between ADHD and GJH/hEDS over time. [11, 18, 27] Larger cohort studies are essential to enhance the generalizability of findings and to explore the shared biological pathways. Investigating the role of collagen synthesis, ANS regulation, and dopaminergic signaling

could reveal novel therapeutic targets. Additionally, studies examining the impact of hormonal fluctuations during puberty, menstruation, and the postpartum period on ADHD and hEDS symptoms may provide valuable insights into the underlying mechanisms [11, 21, 42]

By advancing our understanding of the neuroconnective phenotype, healthcare providers can bridge the divide between psychiatric and physical medicine, offering holistic care to unique population of ADHD and hEDS individuals.

Conclusions

This review underscores a significant association between ADHD and hypermobility-related disorders, particularly hEDS and symptomatic GJH, emphasizing the intertwined nature of physical and neurodevelopmental health. Recognizing these associations could enhance diagnostics and foster integrative treatment strategies. [21, 39] Alongside biological mechanisms underpinning this connection, the effectiveness of the interventions addressing both physical and neurocognitive symptoms, should be prioritized in future studies. Enhanced understanding of this neuroconnective phenotype may contribute to bridging the gaps between psychiatry and physical medicine, providing comprehensive care for affected individuals in the future. [20, 21, 22]

Author's contribution

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supervision, Czyz Wojciech;

project administration, Wojcikiewicz Michalina;

All authors have read and agreed with the published version of the manuscript.

Funding Statement

The autors declare no funding in relation to this study.

Institutional Review Board Statement

Non applicable

Data Availability Statement

In this section, please provide details regarding where data supporting reported results can be found, including links to publicly archived datasets analyzed or generated during the study. Please refer to suggested Data Availability Statements in section “Research Data Policies”. You might choose to exclude this statement if the study did not report any data.

Conflict of Interest Statement

The autors declare no conflicts of interest in relation to this study.

Declaration of the use of generative AI and AI-assisted technologies in the writing process

In preparing this work, the authors used OpenAI (ChatGPT) for the purpose of grammar and spelling check. After using this tool/service, the authors have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

Disclosure*

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