THE RELATIONSHIP BETWEEN GENERALISED JOINT HYPERMOBILITY AND NEURODEVELOPMENTAL DISORDERS

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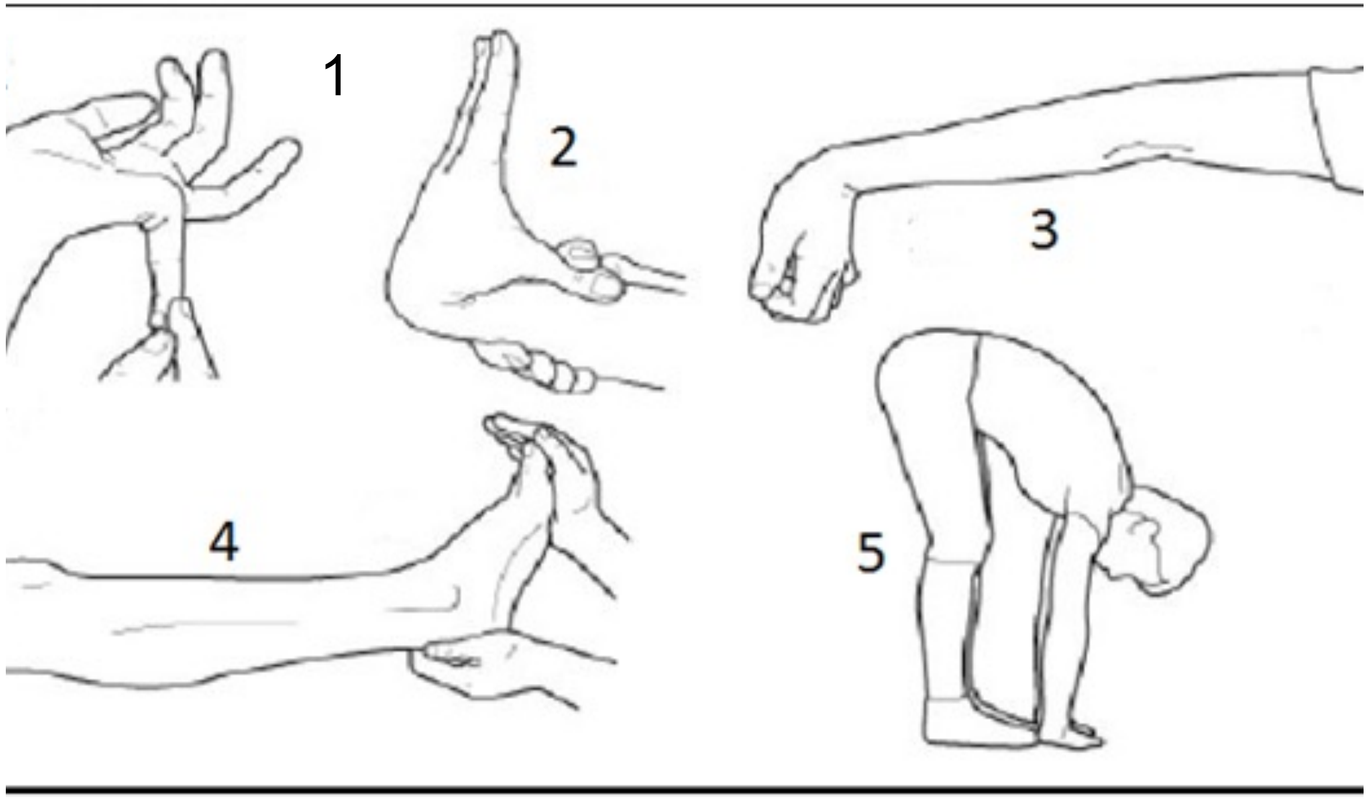
GENERALISED JOINT HYPERMOBILITY 10-20%

HSD 1-2%

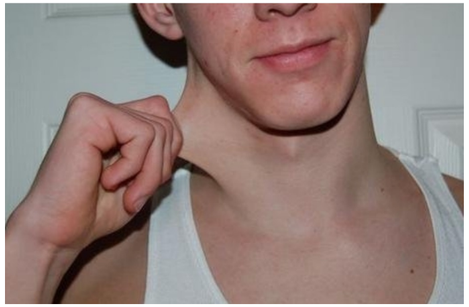
The Beighton Score[1]: ≥ 5/9 18-50 yrs, ≥4/9 50 yrs[2]

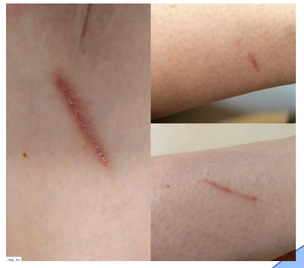


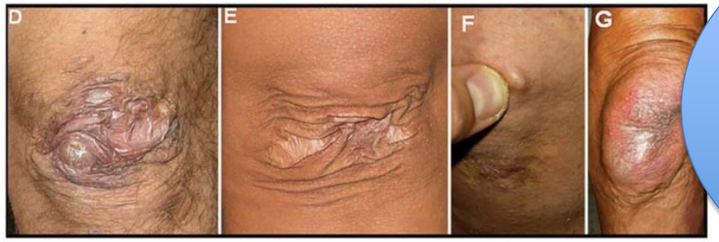
HYPERMOBILITY SPECTRUM DISORDERS

1. Beighton P, Solomon L, Soskolne CL. Articular mobility in an African population. *Ann Rheum Dis* (1973)
2. Malfait F et al. The 2017 international classification of the Ehlers-Danlos syndromes. *Am J Med Genet Part C Semin Med Genet* (2017)

EHLERS-DANLOS SYNDROMES







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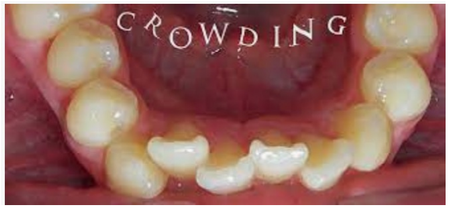
WILEY

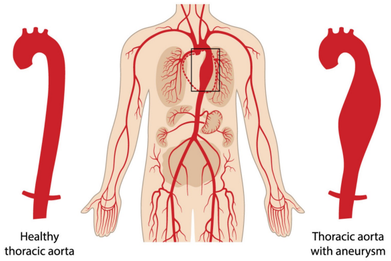
Joint Hypermobility

Skin

Tissue fragility

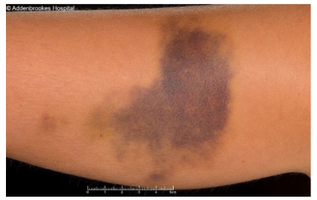


Thoracic Aortic Aneurysm



Healthy thoracic aorta

Thoracic aorta with aneurysm



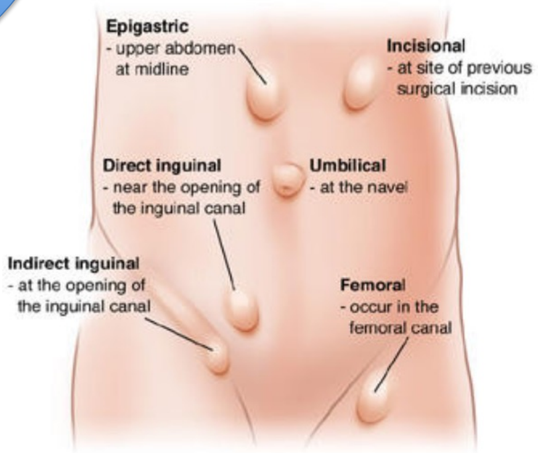
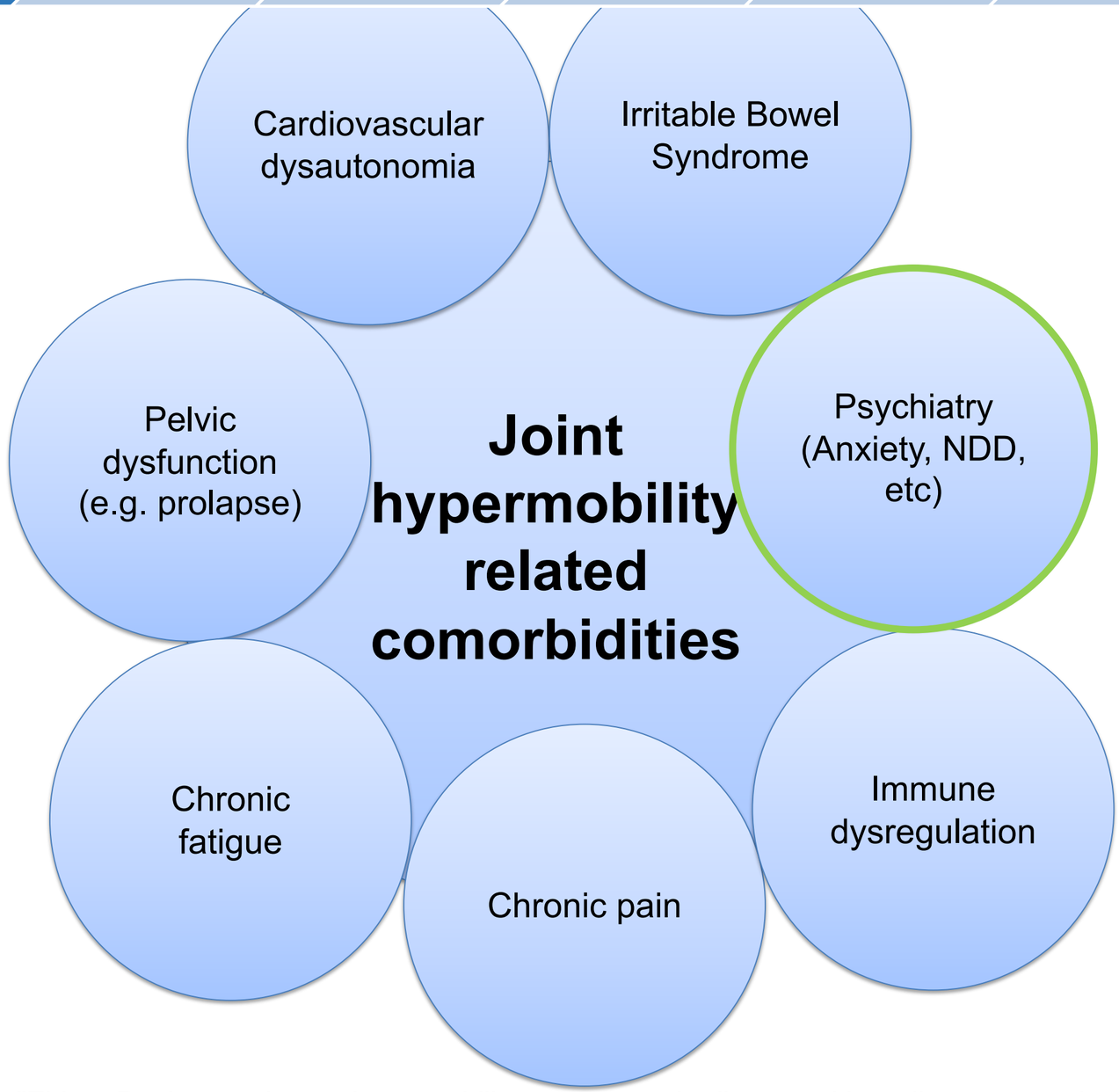


Table 4. New classification of the Ehlers–Danlos syndromes

New classification	Previous classification	Inheritance	Genes	Prevalence[a]	Major distinguishing features
Classical	Classic	AD	*COL5A1, COL5A2, COL1A1* (rare)	1/20 000	Papyraceous and hemosiderotic scars Velvety, hyperextensible skin
Classical-like	Tenascin XB-deficient	AR	*TNXB*	24 pts	Velvety, hyperextensible skin
Cardiac-valvular	Cardiac-valvular	AR	*COL1A2*	6 pts	Severe cardiac valvular involvement Velvety, hyperextensible skin
Vascular	Vascular	AD	*COL3A1, COL1A1* (rare)	No less than 1/200 000	Extensive easy bruising Vascular accidents/ruptures
Hypermobile	Hypermobility	AD	None	No less than 1/5000	Musculoskeletal pain Dislocations
Arthrochalasia	Arthrocalasia	AD	*COL1A1, COL1A2*	49 pts	Marked joint hypermobility Bilateral hip dysplasia
Dermatosparaxis	Dermatosparaxis	AR	*ADAMTS2*	15 pts	Extreme skin fragility Velvety, hyperextensible skin
Kyphoscoliotic	Kyphoscoliotic type 1	AR	*PLOD1*	84 pts (*PLOD1*) and 10 pts (*FKBP14*)	Congenital, progressive scoliosis Congenital hypotonia
	Kyphoscoliotic type 2	AR	*FKBP14*		
Brittle cornea syndrome	Brittle cornea syndrome type 1	AR	*ZNF469*	51 pts	Thin cornea Early-onset ketatoconus/globus
	Brittle corna syndrome type 2	AR	*PRDM5*		
Spondylodysplastic	Progeroid type 1	AR	*B4GALT7*	7 pts (*B4GALT7*), 47 pts (*B3GALT6*) and 8 pts (*SLC39A13*)	Short stature Congenital hypotonia Limb bowing
	Progeroid type 2	AR	*B3GALT6*		
	Spondylocheiro-dysplastic	AR	*SLC39A13*		
Musculocontractural	Musculocontractural type 1 or Kosho type	AR	*CHST14*	39 pts (*CHST14*) and 3 pts (*DSE*)	Velvety, hyperextensible skin Congenital contractures Facial features
	Musculocontractural type 2	AR	*DSE*		
Myopathic	Myopathy overlap	AD or AR	*COL12A1*	9 pts	Congenital hypotonia Proximal contractures
Periodontal	Periodontal	AD	*C1R, C1S*	>100 pts	Severe, early-onset periodontitis Tibial plaques

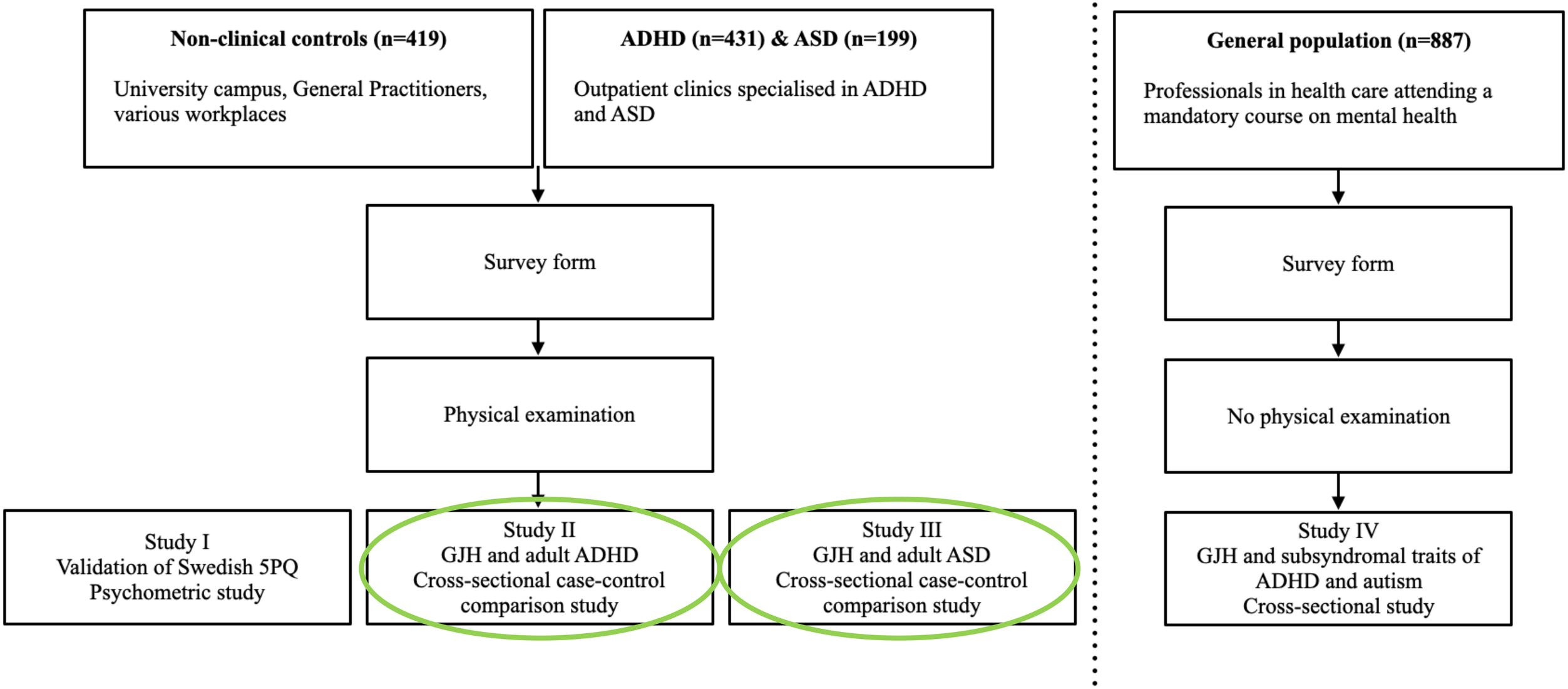
Castori M, Hakim A. Contemporary approach to joint hypermobility and related disorders. *Curr Opin Pediatr* (2017)



1. Castori, Marco. "Ehlers-Danlos syndrome, hypermobility type: an underdiagnosed hereditary connective tissue disorder with mucocutaneous, articular, and systemic manifestations." *International Scholarly Research Notices* (2012)
2. Castori M, Hakim A. Contemporary approach to joint hypermobility and related disorders. *Curr Opin Pediatr* (2017)

Varför?

- Gemensam etiologi/patogenes?
  - Gener som kodar för kollagen är också involverade i utveckling/funktion av CNS?
- Möjliggöra tidigare diagnos och behandling
  - Smärta, ledinstabilitet, fatigue etc -> Fysio- och arbetsterapi
- GJH som en biomarkör
  - Kliniskt relevant subgrupp inom psykiatrin?


Non-clinical controls (n=419)
University campus, General Practitioners, various workplaces
ADHD (n=431) & ASD (n=199)
Outpatient clinics specialised in ADHD and ASD
General population (n=887)
Professionals in health care attending a mandatory course on mental health
Survey form
Survey form
Physical examination
No physical examination
Study I
Validation of Swedish 5PQ
Psychometric study
Study II
GJH and adult ADHD
Cross-sectional case-control comparison study
Study III
GJH and adult ASD
Cross-sectional case-control comparison study
Study IV
GJH and subsyndromal traits of ADHD and autism
Cross-sectional study

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Association between adult attention-deficit hyperactivity disorder and generalised joint hypermobility: A cross-sectional case control comparison

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Comorbidity
Hypermobility
Joint instability
Ehlers-Danlos syndrome

ABSTRACT

Growing evidence suggests an unexpected association between generalised joint hypermobility (GJH) and several psychiatric conditions, and a shared pathophysiology has been proposed. No previous studies on adult attention-deficit/hyperactivity disorder (ADHD) are available. This study aimed to evaluate the association between adult ADHD and GJH. A total of 431 adults with ADHD and 417 non-ADHD controls were included in this cross-sectional comparative study. GJH was assessed by physical examination following the Beighton scoring system (BSS). Furthermore, musculoskeletal symptoms and skin abnormalities were queried to create a proxy for *symptomatic* GJH (e.g., Hypermobility spectrum disorders and Ehlers-Danlos syndrome) to differentiate this from *non-specified* GJH defined by BSS only. Logistic regression examined the influence of ADHD and candidate covariates (age, sex, ethnicity) on GJH and symptomatic GJH, respectively. ADHD was significantly associated with GJH, as defined by the BSS, with adjusted odds ratios of 4.7 (95% confidence interval [CI] 3.0–7.2, $p < .005$). Likewise, ADHD was significantly associated with symptomatic GJH, as defined by the BSS and additional symptoms, with adjusted odds ratios of 6.9 (CI 95% 4.1–11.9, $p < .005$). Our results suggest that GJH may represent a marker for an underlying systemic disorder involving both connective tissue and the central nervous system. GJH with additional musculoskeletal symptoms and/or skin abnormalities has a considerable stronger link to adult ADHD than non-specified GJH has, and may need awareness in ADHD management. Future studies should investigate the mechanisms behind this association and how comorbid GJH affects ADHD outcome.

Prevalence comparisons

	ADHD	Non-ADHD	p
Generalised joint hypermobility			
Women	37%	11%	.00
Men	12%	5%	.02
Symptomatic generalised joint hypermobility			
Women	32%	7%	.00
Men	9%	2%	.00

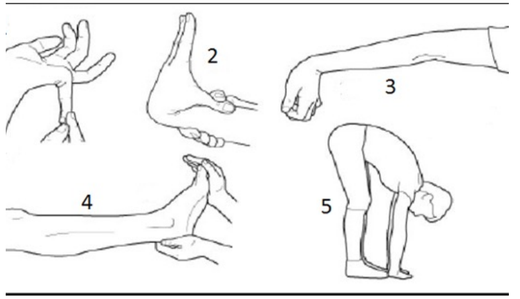
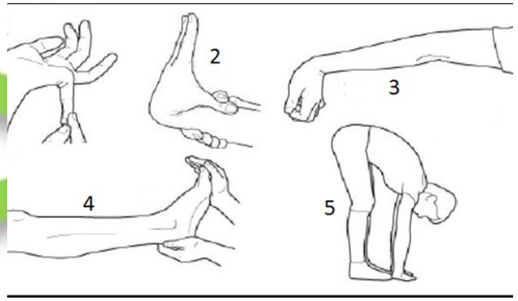


Table 3
Results of the logistic regression models on ADHD diagnosis effect on generalised joint hypermobility.

	Unadjusted models						Adjusted models					
Predictor	B	SE	Wald	*df*								
GJH as defined by the BSS[a]												
ADHD	1.45	.212	46.6	1		4.65 (3.01–7.18)						
Sex												
Age												
Ethnicity												
Model	$\chi^2(1) = 53.02$, $p < .001$											
GJH as defined by the 5PQ[b]												
ADHD	.639	.144	19.7	1	.000	1.89 (1.43–2.51)	.619	.148	17.6	1	.000	1.86 (1.39–2.48)
Sex							.915	.158	33.7	1	.000	2.50 (1.83–3.40)
Age							-.008	.006	1.78	1	.182	.992 (.980–1.00)
Ethnicity												
Model	$\chi^2(1) = 20.00$, $p < .001$											
Symptomatic[c] GJH-BSS												
ADHD	1.88	.266	49.8	1		6.94 (4.05–11.9)						
Sex												
Age												
Ethnicity												
Model	$\chi^2(1) = 63.94$, $p < .001$											
Symptomatic GJH-5PQ												
ADHD	1.00	.159	39.9	1	.000	2.73 (2.00–3.72)	.979	.162	36.6	1	.000	2.66 (1.94–3.65)
Sex							.881	.174	25.7	1	.000	2.41 (1.72–3.40)
Age							.001	.007	.007	1	.935	1.00 (.988–1.01)
Ethnicity							.151	.179	.709	1	.400	1.16 (.818–1.65)
Model	$\chi^2(1) = 41.82$, $p < .001$				Nagelkerke $R^2 = 7.0\%$		$\chi^2(4) = 70.37$, $p < .001$				Nagelkerke $R^2 = 11.5\%$	



frontiers in Psychiatry

ORIGINAL RESEARCH
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The Relationship Between Generalised Joint Hypermobility and Autism Spectrum Disorder in Adults: A Large, Cross-Sectional, Case Control Comparison

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Autism spectrum disorder (ASD) and generalised joint hypermobility (GJH) share a number of clinical manifestations including proprioceptive impairment, motor difficulties, sensory hypersensitivity, and autonomic dysfunction. Clinical observations suggest that GJH is overrepresented in ASD. However, there are currently few systematic studies available. Knowledge about comorbidities may unfold common aetiopathological pathways underlying the association and improve the clinical management. The aim of this large, cross-sectional comparative study is to evaluate the relationship between ASD and GJH in adults. Data on joint hypermobility, symptoms associated with both hypermobility spectrum disorders (HSD) and hypermobile Ehlers-Danlos syndrome (hEDS), lifetime psychiatric diagnoses, psychiatric rating scales for ASD and attention deficit hyperactivity disorder (ADHD), and socio-demographics was collected for 199

METHODS -PAPER III

Case-control comparison:

- 199 adults with ASD (95 women, 104 men)[a]
- 419 non-ASD controls (246 women, 173 men)[b]

[a] Comorbid ADHD was allowed

[b] The same community sample as studies II and III

Procedure:

- Survey form
- Physical examination for GJH
- Proxy for symptomatic-GJH

Statistics:

- Prevalence comparisons
- Logistic regression models adjusting for age, sex and ethnicity

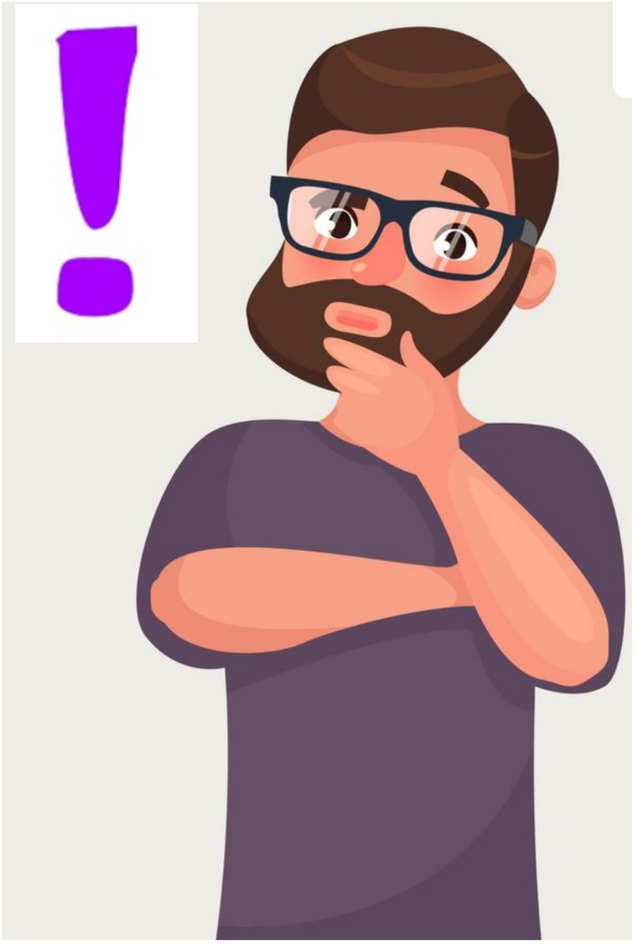
Logistic regression for ASD and GJH (comorbid ADHD allowed)
(adjusting for age, sex and race)

	p	Adjusted OR
Generalised joint hypermobility	<.01	**3.1** (1.9-5.2)
Symptomatic generalised joint hypermobility	<.01	**4.9** (2.6-9.0)

ADHD cohort (Study II)	p	Adjusted OR
Generalised joint hypermobility	.00	**4.7** (3.0-7.2)
Symptomatic generalised joint hypermobility	.00	**6.9** (4.1-12)

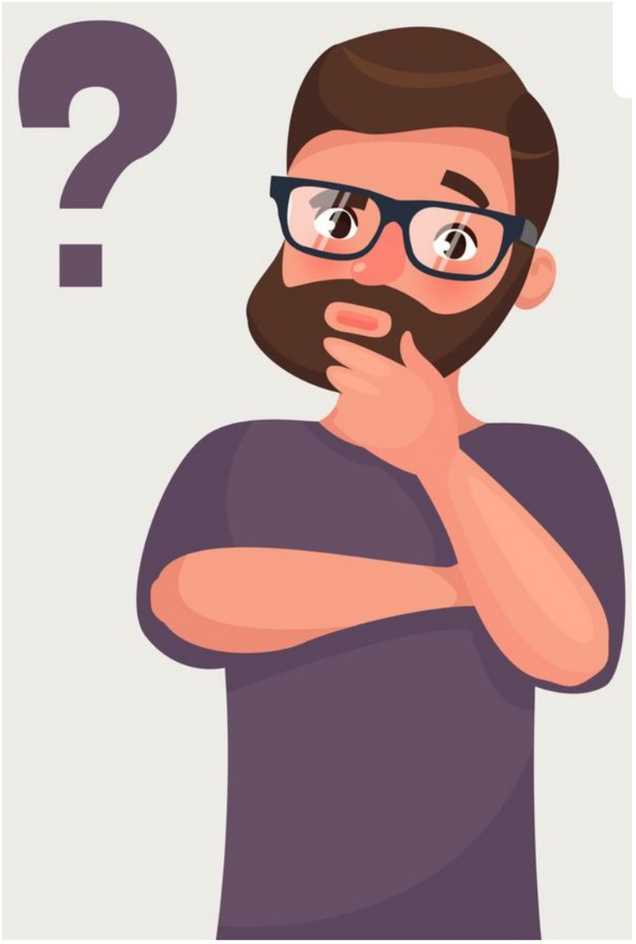
BETYDELSE

- Styrkor
  - Största studier hittills som mätte GJH hos alla deltagare
  - Sample size möjliggjorde justerade analyser
  - Undersöka sambandet från olika vinklar
    - Överrörliga kohorter (HSD, EDS)
    - Psykiatriska kohorter
- Association mellan ADHD och GJH börjar bli robust
- Ökad evidens för association mellan Autism och GJH
- Intressant att ett samband för ”den ospecifika” variabeln GJH



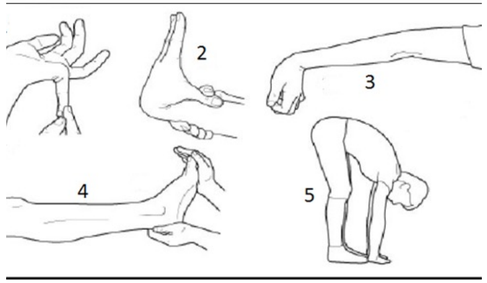
EJ KLARLAGT

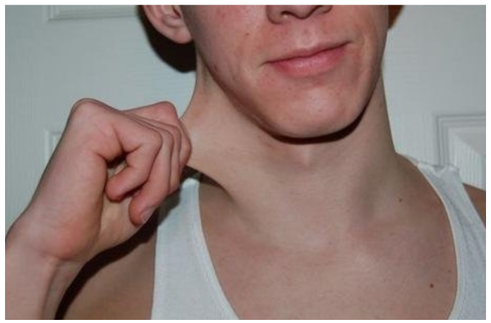
- Om att ha en ADHD fenotyp är drivande
- Om komorbid GJH påverkar klinisk outcome
  - GJH som en relevant biomarkör
  - Symptomkluster av GJH, ESSENCE, ångest?
    - Dysautonomi? Långsam upptrappning CS?
    - Behov av fysio- och arbetsterapi?
- Bakomliggande orsak till sambandet
  - Gemensam etiologi/patologi?

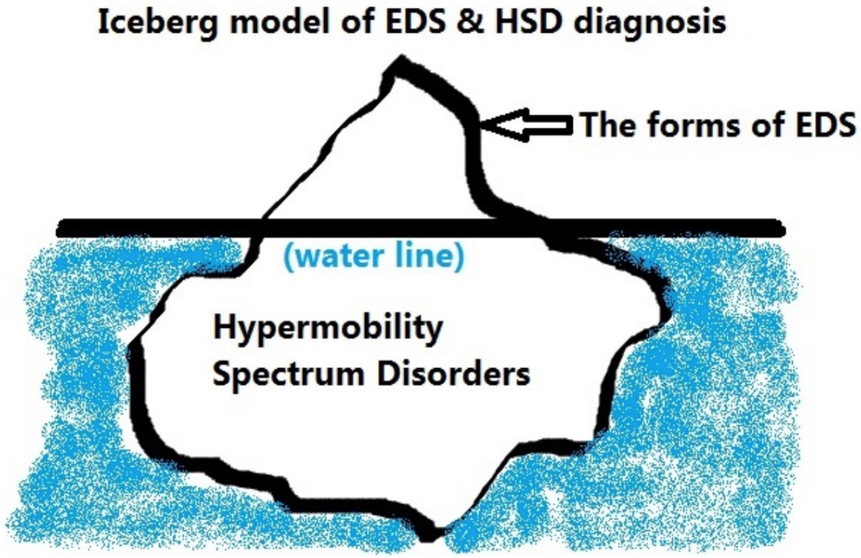


TAKE HOME MESSAGES

- Känna till överrörlighetssyndrom
  - GJH
  - HSD
  - Ehlers-Danlos







- Mycket forskning kring associationer
  - Håll er ajour (Men var kritiska)

- Robust evidens för GJH och ångest samt ADHD

VIDARE LÄSNING

Artiklar finns som open-source

Avhandling att ladda ned på DIVA

DiVA portal
http://oru.diva-portal.org

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Co-supervisor: **Marie Elwin**

Co-author: **Mats B. Humble**

Co-author: **Nils Thelin**

Idea/inspiration: **Olle Hollertz**

All study participants and staff who facilitated data collection

The Swedish 5PQ

Namn: Ålder: Kön:

Datum: Ansvarig:

Besvara frågorna utifrån vad som känns sant för dig. Sätt kryss i endast en ruta per fråga!

		NEJ	JA
1.	Kan du nu (eller har du någonsin kunnat) placera händerna platt på golvet utan att böja knäna?	☐	☐
2.	Kan du nu (eller har du någonsin kunnat) böja tummen så att den nuddar din underarm?	☐	☐
3.	Underhöll du dina vänner med att vrida din kropp i konstiga ställningar eller kunde du gå ner i split som barn?	☐	☐
4.	Har din knäskål eller axel gått ur led mer än en gång som barn eller tonåring?	☐	☐
5.	Anser du dig själv vara påtagligt överrörlig i lederna?	☐	☐

- ≥ 2 poäng tyder på generalised joint hypermobility (GJH).
- The Swedish 5PQ uppnådde en sensitivitet på 91%, en specificitet på 75% och en area under the curve på 0.87.