BJPsych Open (2017)
3, 236–242. doi: 10.1192/bjpo.bp.116.004325

Generalised joint hypermobility and neurodevelopmental traits in a non-clinical adult population

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Background
Generalised joint hypermobility (GJH) is reportedly overrepresented among clinical cases of attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and developmental coordination disorder (DCD). It is unknown if these associations are dimensional and, therefore, also relevant among non-clinical populations.

Aims
To investigate if GJH correlates with sub-syndromal neurodevelopmental symptoms in a normal population.

Method
Hakim-Grahame's 5-part questionnaire (5PQ) on GJH, neuropsychiatric screening scales measuring ADHD and ASD traits, and a DCD-related question concerning clumsiness were distributed to a non-clinical, adult, Swedish population (*n*=1039).

Results
In total, 887 individuals met our entry criteria. We found no associations between GJH and sub-syndromal symptoms of ADHD, ASD or DCD.

Conclusions
Although GJH is overrepresented in clinical cases with neurodevelopmental disorders, such an association seems absent in a normal population. Thus, if GJH serves as a biomarker cutting across diagnostic boundaries, this association is presumably limited to clinical populations.

Declaration of interest
None.

Generalised joint hypermobility (GJH) is a condition characterised by the ability to extend several synovial joints beyond their normal limits.[1] GJH is a key feature among a number of heritable connective tissue disorders including Ehlers–Danlos syndrome (EDS). Its presence is one of the necessary criteria for diagnosis of the hypermobility type of EDS (hEDS)[2] but, in addition, GJH commonly occurs without the other necessary features of hEDS. The prevalence of GJH depends on age, gender, ethnicity and the criteria used to define it. It is usually reported to range between 10 and 20% in the general population, although a wide variation exists.[3] Many individuals with GJH are asymptomatic, which contributes to difficulties in reports of prevalence, as these are not recorded in the healthcare system. GJH diminishes with age, is about three times more common in females than males and is more common in Asian and African populations compared to Caucasians.[3]

Identifying GJH

There is a variation in definition as well as a lack of consensus on tests and criteria for GJH.[1] The Beighton 9-point scoring system[4] is the most commonly used; however, cut-off levels vary, being either 4/9, 5/9 or 6/9.[1] Hakim-Grahame's 5-part questionnaire on joint hypermobility (5PQ),[5] described below and shown in Table 1, is regarded as a valid tool when screening for GJH.[1,3]

Somatic and psychiatric symptoms associated with GJH

GJH has been linked with a number of somatic symptoms such as musculoskeletal pain, migraine, gastro-intestinal symptoms and postural tachycardia.[2] Among researchers, the interest in GJH among psychiatric patients in general has increased more recently. Three systematic reviews have been published on the possible links between GJH and psychiatric disorders.[6–8] They report the strongest link with anxiety, but also possible associations with a number of other psychiatric conditions such as depression, schizophrenia, eating disorders, personality disorders, substance use disorders and lifetime neurodevelopmental disorders (e.g. attention deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and developmental coordination disorder (DCD)). Most research on neurodevelopmental associations with GJH has been done in the area of ADHD and DCD, with some smaller studies and case reports on ASD. Certainly more research is needed to consider these associations firmly established.[8] As DCD is characterised by motor coordination difficulties and clumsiness, the link between GJH and DCD may be indirect; impaired proprioception has been suggested to mediate this association.[9] Further support for a link between GJH and neurodevelopment is a reported association between GJH and problems related to Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE).[10] Concerning possible psychiatric manifestations related to GJH in non-clinical populations, we know only of three studies, all investigating the relationship between anxiety and GJH in adult populations.[11–13] These three studies all revealed positive, although very weak, associations between GJH and anxiety, which suggest that GJH may represent a dimensional trait, associated with anxiety in the general population. We hypothesised that, similarly, the association between GJH and neurodevelopmental traits would extend to a non-clinical population and perhaps serve as a dimensional biomarker.

Table 1 The Five-Part Hakim-Grahame Questionnaire (5PQ)[5] for defining Generalised Joint Hypermobility (GJH)

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child did you amuse your friends by contorting your body into strange shapes OR could you do the splits?
4. As a child or teenager did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself double-jointed?
Endorsement of two or more questions suggests GJH.

The aim of this study

The aim of this study was to evaluate whether there is an association between reported GJH traits and reported traits suggestive of ADHD, ASD or DCD among non-clinical Swedish adults, bridging clinical and non-clinical populations. Our hypothesis was that those classified as GJH should report more pronounced traits related to these neuropsychiatric disorders, when compared to those without GJH.

Method

Participants

A total of 1039 professionals completed a questionnaire and provided demographic data while attending a mandatory course on mental health. The lectures were given on seven different occasions throughout Sweden from May 2014 until December 2014. During the course, attendees were invited to participate in the study by responding anonymously to the questionnaire. They were informed that the aim was to collect data on joint mobility and neuropsychiatric traits from a community population, which they themselves represented. They were professionals within the education, community health, local government or mental health sectors. The only exclusion criteria applied were previous or present diagnosis of ADHD or ASD and not matching the age criterion, 18–65 years. The study was approved by the medical ethical review board in Stockholm, Dnr. 2014/1742-31.

Questionnaire

To study symptoms of GJH, ADHD and ASD, we used validated instruments described below. We also included questions about lifetime presence of joint disorders ('Have you been diagnosed with any joint disorder, that is, rheumatoid arthritis? If yes, which one?'), diagnoses of ADHD ('Have you been diagnosed with ADHD or ADD?'), ASD ('Have you been diagnosed with autism, atypical autism or Asperger syndrome?'), depression ('Have you been diagnosed with depression?') and other psychiatric disorders ('Have you been diagnosed with any other psychiatric disorder? If yes, which disorder?'; this particular question was added at a later stage of the study; thus, not all participants were asked about other psychiatric disorders). Anxiety disorders were identified by examining free text responses to the item 'other psychiatric disorder' independently by two of the authors. Moreover, we included a preliminary version of the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0, not presented here), and questions on academic performance and bullying. This last item has been used in previous studies with comparable populations.[14,15] In one study including 2600 participants with a gender distribution similar to this study, bully victimisation was reported in 29%.[15] We assumed that if the rate of bullying remained consistent across studies, this would support the validity of our measures.

Generalised joint hypermobility

We used the 5PQ,[5] shown in Table 1, to define GJH. It includes five statements; each affirmative answer is scored as 1 point, resulting in scores between 0 and 5. Using the recommended cut-off of ≥2, it has a reported sensitivity of 80–85% and a specificity of 80–89%.[5,16] The same cut-off score is used for both men and women.[5] When the 5PQ was validated against the Beighton score on a healthy Swedish population (n=141) in similar test circumstances as the target population, the sensitivity was 72% and specificity was 80% (manuscript in preparation).

Attention-deficit hyperactivity disorder

Symptoms of ADHD were determined by using the ASRS rating scale (ASRS-v1.1).[17] It consists of 18 items rated from 'Never' to 'Very often' on a Likert scale (range 0–4). ASRS includes two subscales: inattention (ASRS Inatt) and the combined subscale on hyperactivity/impulsivity (ASRS Hy/Imp). The scores of the total scale range 0–72, each subscale 0–36. A significant correlation (r=0.43) between total scores and clinical symptom severity has been shown,[17] supporting the use of a continuous scoring method for measuring traits of ADHD. In a Norwegian study of a non-psychiatric population, ASRS mean score was 23.5 in men and 22.2 in women.[18]

Autism spectrum disorder

Autistic traits were assessed using the AQ-10 consisting of 10 items on a 4-point response scale.[19] It is an abridged version of the 50-item Autism Spectrum Quotient (AQ).[20] The recommended use of AQ-10 in clinical samples is to dichotomise the scores on each item into either 'agree' responses (yielding 1 point) or 'disagree' responses (yielding 0), leading to a total range of 0–10. We chose to use a continuous scoring of 0–3 for each item, enabling a total range of 0–30. This method is recommended for the full AQ version when used to asses traits of ASD in non-clinical samples.[21] Some items are reversed on the AQ-10, and these are coded such that higher scores represent more pronounced autistic trait.

Clumsiness suggestive of DCD traits

Signs of clumsiness were determined by one single question; 'In elementary school (when you were about 12 years), did you perform worse than average in physical education (i.e. ball games, coordination, agility)?' with the response alternatives 'yes' and 'no'. This method has been applied in earlier studies on normal populations and has provided consistent results with approximately 18% affirmative responses.[14,15]

Statistics

Statistical analyses were conducted in IBM SPSS statistics version 23. The sample was divided into two groups: hypermobile and non-hypermobile according to the 5PQ. To compare ASRS and AQ-10 scores between the two groups, we used Student's t-test. If *post hoc* testing caused smaller samples, deviating from the normal distribution, a supplementary Mann–Whitney U-test was performed. If both methods produced similar results, we chose only to present Student's t-test. Pearson's chi-squared test was used for the dichotomous item on motor skills and psychiatric disorders. Exploratory *post hoc* analyses were performed on neuropsychiatric traits for different subgroups, age groups and for different cut-off levels on the 5PQ. We also performed *post hoc* analyses on reported diagnosis of anxiety and depression in relation to hypermobility. We report 2-tailed P-values. None of the reported P-values has been adjusted for multiple testing.

We only allowed missing items in the 5PQ if the participant scored ≥2 (≥3 and ≥4 in *post-hoc* analyses described above) and consequently would have been categorised as hypermobile

regardless of missing data. For the ASRS analyses, we allowed one missing item from each subscale. In such cases, we used the mean substitution method. For the AQ-10, the motor skill item and reported diagnoses of anxiety and depression we did not allow any missing data. Missing data on age, gender or previous diagnosis of ADHD or ASD were additional reasons for exclusion.

Results

Sample characteristics

The included population consisted of 734 women (82.8%) and 153 men (17.2%), with a mean age of 45 years (range 18–65 years). All were employed professionals. Sixty-two individuals (6.9%) had at least one parent with origin outside Northern Europe (missing data for 11 individuals). Thirty-two individuals (3.6%) endorsed being diagnosed with ADHD or ASD or did not respond to this question, thus were excluded from the study (see flowchart, Fig. 1).

In total, 157 (17.7%) endorsed having been diagnosed with clinical depression (missing data for six individuals). Out of the 534 individuals that were asked if they had 'other psychiatric disorders', 4.5% (*n*=24) answered in affirmative to this question (missing data for four individuals) (Table 2).

Hypermobility and neuropsychiatric traits

In the entire sample, *n*=287 (32.4%) endorsed two or more items on the 5PQ, suggesting GJH in accordance with our criteria, whereas 600 (67.6%) did not. As expected, GJH was more frequent among women (34.5%) than among men (22.2%). The hypermobility rates according to different 5PQ cut-offs are presented in Table 2. Mean scores on ASRS were 25.2 (s.d.=8.1), with no difference between females (25.5 (s.d.=8.0)) and males (24.1 (s.d.=8.4); t_{880}=1.9, *P*=0.06); while those for AQ-10, 8.6 (s.d.=3.4) in the whole group, differed between females (8.5 (s.d.=3.3)) and males (9.4 (s.d.=3.5); t_{843}=2.9, *P*=0.004). In total, 12.1% reported having been poorer than average in academic skills, and 14.3% endorsed having been poorer than average in physical education. In total, 28.4% reported having been bullied in school.

Table 2 Demographics of the sample including prevalence of reported psychiatric disorders and hypermobility

	Females *N*=734	Males *N*=153
Age, mean (s.d.)	44.7 (10.4)	44.2 (11.0)
5PQ=0 (%)	237/734 (32.3)	67/153 (43.8)
5PQ=1 (%)	244/734 (33.2)	52/153 (34.0)
5PQ≥2 (%)	253/734 (34.5)	34/153 (22.2)
5PQ≥3 (%)	116/716 (16.2)	11/152 (7.2)
5PQ≥4 (%)	51/710 (7.2)	4/152 (2.6)
5PQ=5 (%)	10/709 (1.4)	2/152 (1.3)
Depression (%)[a]	143/728 (19.6)	14/153 (9.2)
Questionnaire version 2[b]	Females *N*=433	Males *N*=101
Anxiety disorders (%)[c]	11/430 (2.5)	1/100 (1.0)
Other psychiatric disorders (%)	10/430 (2.3)	2/100 (2.0)

a. ('Have you been diagnosed with depression?')
b. In a later stage of the study, a question about non-depressive psychiatric disorders was added. ('Have you been diagnosed with any other psychiatric disorder? If yes, which disorder?')
c. Anxiety disorders were identified by examining free text responses to the item 'other psychiatric disorder' independently by two of the authors.
Missing data: 6 women did not respond to whether they had a history of depression. Out of the individuals completing the second version of the questionnaire, 3 women and 1 man did not respond to whether they had other psychiatric disorders. Regarding the 5PQ questionnaire 25 women and 1 man had one or more missing items.

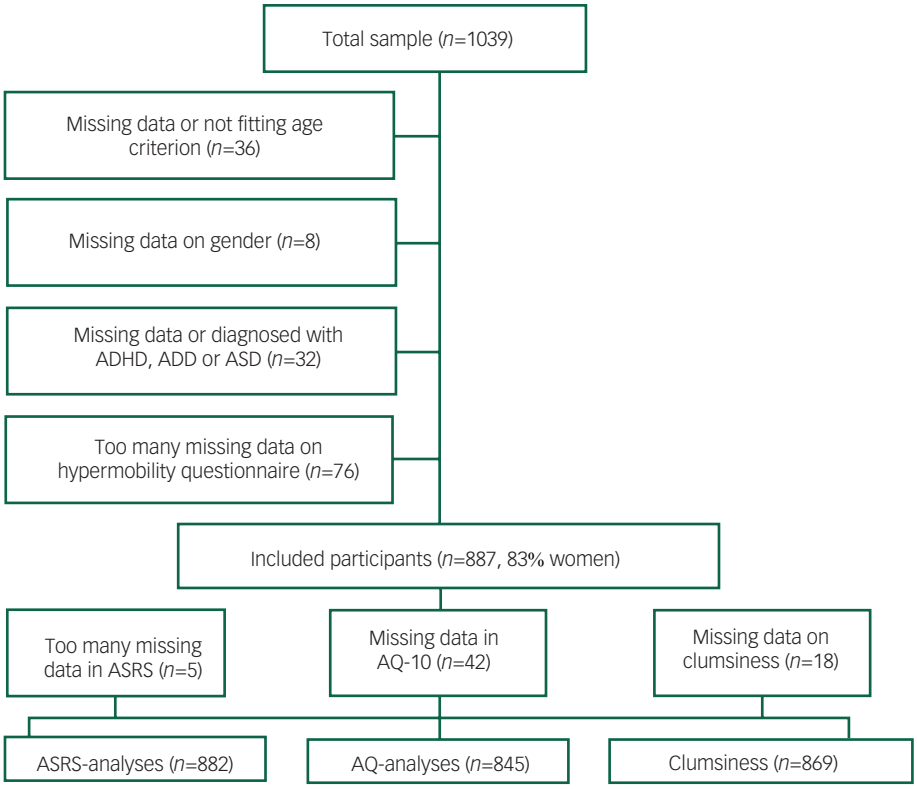

Fig. 1 Study population.

Table 3 The association between self-rated neurodevelopmental symptoms (i.e. ADHD, autism spectrum disorder (ASD) and clumsiness) and self-reported generalised joint hypermobility (GJH) traits in a non-clinical adult Swedish population

Neuro-developmental traits		Hypermobile[a]	Not hypermobile	*t*	d.f.	*P*
ASRS total score, mean (s.d.)	Men (*n*=152)	25.2 (9.36)	23.8 (8.11)	0.82	150	0.41
	Women (*n*=730)	25.9 (8.20)	25.3 (7.90)	0.97	728	0.33
AQ-10 total score, mean (s.d.)	Men (*n*=144)	10.2 (3.89)	9.14 (3.35)	1.46	142	0.15
	Women (*n*=701)	8.46 (3.31)	8.47 (3.35)	–0.04	699	0.97
				χ^2	d.f.	*P*
Clumsiness, (yes/no)[b]	Men (*n*=152)	33 (3/30)	119 (7/112)	0.43	1	0.51
	Women (*n*=717)	247 (34/213)	470 (80/390)	1.28	1	0.26

ASRS, Adult ADHD Self Report Scale, continuous scoring method (0–4 on each item).
AQ-10, Autism quotient abridged 10-item version, continuous scoring method (0–3 on each item).
a. Endorsement of two or more items in the 5PQ.
b. Clumsiness defined as reported performance below average in physical education in school at age 12 years ('In elementary school (when you were about 12 years), did you perform worse than average in physical education (i.e. ball games, coordination, agility)?'). A yes response suggests clumsiness, whereas a no response does not.

Because of the gender difference of GJH endorsement, we analysed associations between GJH and neuropsychiatric traits separately for men and women. However, no significant differences emerged in any of these primary analyses. Mean values of the ASRS and AQ-10 scores and endorsement of clumsiness in relation to GJH in men and women, respectively, are shown in Table 3.

Post hoc analyses

Neuropsychiatric traits and age

When groups were divided according to age, women 45 years and younger, with 5PQ cut-off of ≥2 had higher ASRS total scores and ASRS Hy/Imp subscale scores compared to those who were not hypermobile (ASRS total 28.0 *v.* 25.7, *P*=0.014 and ASRS Hy/Imp 14.0 *v.* 12.4 *P*=0.004). No significant results emerged for men (data supplement Table DS1). For AQ and clumsiness, no significant associations were revealed with hypermobility (Tables DS4–DS8) excluding a negative association between clumsiness and hypermobility for women aged 46–65 (*P*=0.1) (Table DS8).

Neuropsychiatric traits and 5PQ-cut-off scores

When a higher 5PQ cut-off (≥4/5) was applied, the extraordinary hypermobile women had higher ASRS total scores and ASRS Hy/Imp subscale scores compared to those not hypermobile irrespective of age (ASRS total 27.8 *v.* 25.1 *P*=0.019 and ASRS Hy/Imp 13.9 *v.* 12.1 *P*=0.010). No significant results emerged for women at the 5PQ cut-off (≥3/5) or for men at any 5PQ cut-off. However, women with 5PQ cut-off=5 (*n*=10) had higher ASRS total and ASRS Inatt score (*P*=0.003 *v.* *P*<0.001) compared with other women. Only two men had the highest cut-off of 5 on the 5PQ, which precluded meaningful statistics (Tables DS2, DS3). For AQ and clumsiness, no significant associations were revealed (Tables DS4–DS8).

Anxiety disorders

Seven out of 134 (5.2%) hypermobile women (5PQ cut-off≥2/5) reported a diagnosis of anxiety disorder compared with 4 out of 296 (1.4%) non-hypermobile women (*P*<0.02). The low number of males reporting anxiety (*n*=1) precluded meaningful statistics for men (Table DS9).

Depression

No differences were found on reported diagnoses of depression between hypermobile (5PQ cut-off≥2/5) and non-hypermobile men or women (Table DS10).

Discussion

In this study, we have collected and analysed data on reported traits of GJH, ADHD, ASD and clumsiness in a non-clinical population. To our knowledge, this is the first study to examine the relationship between these parameters in a normal population sample. Contrary to our hypothesis, we did not find any relationship between GJH and neurodevelopmental traits, nor between GJH and clumsiness in our primary analyses.

Biomarkers as tools to characterise psychiatric diagnoses

Biomarkers are biological features that may constitute useful tools when searching for aetiology, pathophysiology, diagnosis and choice of treatment. However, regarding psychiatric disorders, a number of obstacles are encountered because of unknown aetiologies and, presumably, a wide heterogeneity in terms of pathophysiology within each diagnosis.[22] Addressing the need of a new approach to classify mental disorders, the National Institute of Mental Health launched the Research Domain Criteria (RDoC) with the specific ambition to assist in identifying psychiatric biomarkers. These would cross the traditional boundaries of nosological classifications and, thus, enable categorisation based on biological findings,[22,23] rather than symptoms alone. Such biomarkers should preferably only exist, or at least be far more common, in the target disorder. Ideally, we should also be able to understand the role of the biomarker in the pathophysiology of the disorder. GJH is a potential candidate for such biomarkers, considering that it has been associated with a number of psychiatric manifestations, for example, clinically diagnosed cases of ADHD, ASD, DCD and anxiety disorders.

Our initial lack of findings in a non-clinical population suggests that this putative relationship is valid only among clinical cases of neurodevelopmental disorders. Nevertheless, in our exploratory *post hoc* analyses, some significant (although quantitatively small) associations emerged, suggesting that more pronounced GJH may indeed be related to hyperactive and impulsive ADHD traits. Among women younger than 45 years, those with hypermobility (5PQ cut-off ≥2) had higher ASRS total scores and Hy/Imp subscale scores compared with the non-hypermobile women. This was also the case for all females regardless of age, when a higher 5PQ cut-off (≥4, a stricter definition of hypermobility) was applied, albeit this difference was small (less than three points on the ASRS). Ten women with the highest 5PQ score, however, were clearly more inattentive and had a high total ASRS score of 32.6, which in fact may suggest an undiagnosed ADHD.

Psychiatric manifestations as part of a systemic disorder

In the case of GJH, it remains largely speculative how it relates to symptoms and pathophysiology of psychiatric disorders. Sinibaldi *et al*[6] discuss several possible mechanisms, including a common process affecting the architecture and function of the musculoskeletal and central nervous systems. Genes coding for extracellular matrix could play a crucial part. The findings by Cederlöf *et al*,[24] an increased risk of psychiatric disorders not only in individuals diagnosed with EDS but also in their unaffected siblings, support a common genetic component. In most EDS subtypes a pathogenic basis, such as genes involved in collagen synthesis, has been identified, but for hEDS, the genetic aetiology remains unclear.[25] In this study, we have focused on individuals with self-reported GJH, not individuals with a diagnosis of EDS. Many individuals with GJH are asymptomatic and would not fulfil the diagnostic criteria for any subtype of EDS, why GJH, presumably, is phenotypically and genetically even more heterogeneous than hEDS. To subgroup GJH, future research may focus on a well-defined EDS population, rather than self-reported GJH. Such a study would tell us if patients with EDS differ from the broader GJH population concerning neuropsychiatric traits.

Anxiety is the psychiatric manifestation with the strongest reported link to GJH. Findings in this study are consistent with the literature, though the strength of this study's finding on anxiety must be considered in the light of the low anxiety prevalence rate reported and the open-ended question utilised for ascertainment ('Have you been diagnosed with any other psychiatric disorder? If yes, which disorder?') with free text utilised to determine anxiety disorder. Structural and functional differences in brain regions associated with anxiety, such as a larger bilateral amygdala volume[26] and an enhanced neural reactivity in insular cortex,[13] have been reported among hypermobile individuals. Furthermore, individuals with GJH often present autonomic dysregulation, resulting in symptoms such as palpitations, chest discomfort and pre-syncopal symptoms such as dizziness and blurred vision.[27] These symptoms are likewise signs of anxiety and often present in panic attacks. However, the direction of causality for the link between hypermobility and anxiety is unsettled.

Limitations

Several limitations of this study deserve mentioning. First, self-reports on psychiatric symptoms and signs of clumsiness were used, and no structured interviews or physical examinations were applied. However, there is no reason to assume that the participants refrained from giving true responses, as all questionnaires were handed in anonymously. Nonetheless, stigma associated with mental health disorders, even on anonymous questionnaires, may have led to underreporting of psychiatric symptoms and to specific psychiatric disorders for the open-ended question ('Have you been diagnosed with any other psychiatric disorder? If yes, which disorder?').

The scales for identifying ADHD and ASD (ASRS and AQ-10) are widely used, but may be over-inclusive if used for diagnosing ADHD or ASD. This is, however, irrelevant to our study, which focused on traits endorsed by people without neurodevelopmental disorders. Furthermore, the normalcy of our sample is supported by the fact that the ASRS mean scores were reported within normal ranges.[18] For AQ-10, a mean score of 2.77 (s.d.=2.0) was reported in a normal population sample, using the dichotomised version.[19] In this study, the dichotomised AQ-10 score was slightly lower, which may be explained by our exclusion of individuals with ASD diagnosis and possibly by the healthcare vocation of most of our individuals.

We acknowledge that assessing DCD traits with one single question about clumsiness (reported performance in physical education compared with peers at 12 years of age) is insufficient. However, as all children with DCD are clumsy, this question is likely to be highly sensitive for traits of DCD, even if diagnostic specificity is lacking. In addition, participants diagnosed with DCD were not specifically excluded in our study. On the other hand, the DCD diagnosis is rarely used as a single diagnosis but mostly applied as comorbidity with other neurodevelopmental disorders.[28] To validate our clumsiness question, we included a question on history of being bullied, which has been used in a previous study.[15] The prevalence rates were almost identical in the two studies. In this study, 14.3% reported being clumsy, which is marginally lower compared with our previous finding, but consistent with the fact that we excluded all participants with diagnoses of ADHD and ASD. Individuals with ADHD and ASD are often clumsy in childhood.[29]

It could be argued that other valid instruments for examining GJH, such as the Beighton score[4] and the Hospital del Mar criteria,[30] are superior to the 5PQ. However, they require a physical examination, which was not feasible in this large population. The validity of the 5PQ has been supported in large populations[31] and a recently published systematic review of clinical assessment methods for classifying GJH concludes that 5PQ is a promising assessment method for population studies.[1] Moreover, as opposed to the Beighton score, the 5PQ does not rely entirely on specific joints being hypermobile and considers previous history of joint hypermobility. Given that joints lose their hypermobility with age,[3] questions on a past history of joint hypermobility allows conclusions regardless of age. Unfortunately, so far, there is no gold standard to define GJH.

Concerning our data on psychiatric diagnoses, validated instruments were not used. However, the reported prevalence of depression accords with estimates in the general population, supporting the validity of our findings.[32] Nonetheless, prospective studies suggest even higher lifetime prevalences.[33] Several potential reasons might explain our low rates on anxiety and other psychiatric disorders. First, participants might have overlooked to report additional psychiatric disorders (i.e. 'Have you been diagnosed with any other psychiatric disorder? If yes, which disorder?') after providing an affirmative response to the prior question on depression. Furthermore, the ambiguous phrasing of this particular question could be interpreted as solely concerning the current disorder. Additionally, the item 'other psychiatric disorders' was not included in the first version of the questionnaire, thus not all participants responded to this question. The main aim of this study was to investigate whether GJH correlates with sub-syndromal neurodevelopmental symptoms in a normal population. We consider the scales used to evaluate traits of ADHD and ASD adequate for this purpose. However, drawing conclusions from our *post hoc* analyses on depression and anxiety disorders may be unjustified, considering the limitations of our data.

The questionnaire was rather extensive. Yet, only between 8 and 12% (depending on the analyses being made) of those reporting age and gender, were excluded because of missing data. The method used to collect data during a daytime course has been shown to result in very low drop-out rates.[14,15]

The vast majority of our participants were women, which is a limitation, as women present a higher prevalence of GJH than men. The use of different cut-off points depending on gender and ethnicity has been discussed but not agreed upon.[1] All self-rated questionnaires on GJH that we are aware of[5,34] apply the same cut-off score for men and women. We included a rather large sample, and the skewed gender distribution did not influence the results when analysed separately for men and women.

In our study, a higher percentage were defined as GJH, compared with most reports among Caucasians.[3] However, the reported prevalence of GJH ranges between 6 and 57% in women and 2 and 35% in men of varying ages and ethnicities.[35] Our high rate could be explained by the fact that the 5PQ considers a lifetime prevalence of joint hypermobility and, therefore, classified more individuals as GJH, compared with the point-prevalences identified in physical examinations. A study including 2600 Caucasian female twins, also using the 5PQ to define GJH, reported a prevalence of 35% among women aged 20–30 years,[16] thus similar to our rates.

To summarise, in a non-clinical, adult Swedish population comparing individuals endorsing or not endorsing GJH traits (broadly defined), we found no difference in self-reported symptoms of ADHD or ASD, nor self-reported childhood clumsiness. This contrasts with the previously reported positive associations, which emerged when clinical samples of ADHD, ASD and DCD cases were investigated. However, in our exploratory *post hoc* testing some significant (although quantitatively small) associations emerged, suggesting that more pronounced GJH may indeed be related to higher ADHD traits.

Thus, the seeming lack of findings in this study does not preclude the possibility of links between GJH and neurodevelopmental disorders. GJH may well serve as a biomarker within the field of neurodevelopmental disorders, but presumably limited to clinical (i.e. more severely affected) populations. According to this study, however, GJH is not a dimensional trait associated with neurodevelopmental symptoms in the general population. Further research is needed, preferably including clinical assessment of GJH to confirm or refute our findings, disentangle possible mechanisms and explore the associations that emerged in our *post hoc* analyses.

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First received 14 Dec 2016, final revision 25 Aug 2017, accepted 29 Aug 2017

Funding

This project was supported by grants from the Swedish Research Council (K2012-62X-22130-04-6). Financial support was also provided through the regional agreement on medical training and clinical research (ALF) between the Stockholm County Council and the Karolinska Institutet. The funders did not interfere with the study design, the data collection, data analysis or manuscript preparation or decisions on the manuscript.

Acknowledgement

We thank all study participants and Gunnar Edman, Sara Ekman and Jonna Eriksson for technical and statistical assistance.

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