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DOI
10.1016/j.gaitpost.2023.01.001

Publication date
2023

Document Version
Final published version

Published in
Gait & Posture

Gait & Posture 100 (2023) 222–229

Contents lists available at ScienceDirect

Gait & Posture

journal homepage: www.elsevier.com/locate/gaitpost

An exploratory study of clinical characteristics and gait features of adolescents with hypermobility disorders

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ARTICLE INFO

Keywords:
Generalized joint hypermobility
Connective tissue disorder
Adolescents
Gait analysis
Functional disability

ABSTRACT

Background: In adolescents with non-pathological and pathological joint hypermobility, gait deviations have been associated with pain and fatigue. It remains unclear what distinguishes the non-pathological form of joint hypermobility (JH) from pathological forms (i.e. hypermobile Ehlers-Danlos syndrome (hEDS) or hypermobility spectrum disorders (HSD). Our objective was to identify discriminative clinical characteristics and biomechanical gait features between adolescents with hEDS/HSD, JH, and healthy controls (HC).

Methods: Thirty-two adolescents were classified into three subgroups (hEDS/HSD=12, JH=5, HC=15). Clinical characteristics (e.g. pain intensity and surface, fatigue, functional disability) were inventoried.

The gait pattern was assessed using a three-dimensional, eight-camera VICON MX1.3 motion capture system, operating at a sample rate of 100 Hz (VICON, Oxford, UK). Spatiotemporal parameters, joint angles (sagittal plane), joint work, joint impulse, ground reaction force and gait variability expressed as percentage using Principal Component Analysis (PCA) were assessed and analysed using multivariate analysis. Multivariate analysis data is expressed in mean differences(MD), standard error(SE) and P-values.

Results: The hEDS/HSD-group had significantly higher fatigue score (+51.5 points, p = <0.001) and functional disability (+1.6, p < .001) than the HC-group. Pain intensity was significantly higher in the hEDS/HSD-group than the other subgroups (JH; +37 mm p = .004, HC; +38 mm, p = .001). The hEDS/HSD-group showed significantly more gait variability (JH; +7.2(2.0)% p = .003, HC; + 7.8(1.4)%, p = <0.001) and lower joint work (JH; −0.07(0.03)J/kg, p = .007, HC; − 0.06(0.03)J/kg, p = .013) than the other subgroups. The JH-group showed significantly increased ankle dorsiflexion during terminal stance (+5.0(1.5)degree, p = .001) compared to hEDS/HSD-group and knee flexion during loading response compared to HC-group (+5.7(1.8) degree, p = .011).

Significance: A distinctive difference in gait pattern between adolescents with non-pathological and pathological joint hypermobility is found in gait variability, rather than in the biomechanical features of gait. This suggests that a specific gait variability metric is more appropriate than biomechanical individual joint patterns for assessing gait in adolescents with hEDS/HSD.

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https://doi.org/10.1016/j.gaitpost.2023.01.001
Received 2 December 2021; Received in revised form 21 December 2022; Accepted 4 January 2023
Available online 5 January 2023

1. Introduction

Joint hypermobility (JH) is present in 7–36% of youth [1–4]. Joint hypermobility is defined as a joint range of movement exceeds the norm for that individual, accounting for age, sex and ethnicity [5]. JH can occur without symptoms [1–4], but may also indicate a serious pathology. In this instance JH can represent both a variation of normality or a symptom rather than a diagnosis [6,7].

In the spectrum of JH, non-pathological and pathological groups are observed. In the non-pathological group, most children do not develop severe musculoskeletal complaints [6] and some even have an advantage of the increased JH [8]. In the pathological group, JH is frequently observed in Hereditary Connective Tissue Disorders (HCTD). HCTDs are characterized by pathological connective tissue fragility in multiple organ systems and can be genetically confirmed, except for hypermobile Ehlers-Danlos syndrome (hEDS) [9] and Hypermobility Spectrum Disorders (HSD) [6]. HSD is the current label for adolescents with JH and musculoskeletal complications such as pain and subluxations, who do not fulfil the criteria for hEDS [6].

Joint pain is a major presenting complaint in adolescents with hEDS/HSD [6,9,10]. In the earliest accounts of Hypermobility Syndrome (HMS) and Ehlers Danlos Type III (EDSIII) (1969, 1971), it has been speculated that joint instability or joint overload may underlie the occurrence and persistence of pain [11]. Later on, with the evolution of the diagnostic criteria this assumption of an intrinsic link between pain and joint biomechanics remains highly suggested by many authors in the field and also is often included as a rationality for treatment [12]. Still over the years only anecdotal evidence has been presented that supports this assumption, nor evidence that refutes.

Chronic fatigue is also frequently reported among adolescents with hEDS/HSD which includes bodily and mental fatigue that only minimally improves with rest [13,14]. Fatigue may also contribute to musculoskeletal pain and muscle weakness and could affect gait [13,15–18]. The relationship between fatigue and gait was previously investigated in adolescents with symptomatic JH [18]. A reduced ground reaction force was observed anda possible connection between fatigue and the loss of proprioceptive acuity in lower limb muscles was suggested [13,15–18].

When considering all of the literature regarding gait, joint biomechanics or motor control, a major limitation to all of these observations is that they focus on a specific joint (for e.g. the knee) or a specific movement of the gait cycle (for e.g. heel strike), and therefore it is not able to regard whole chain of movements and biomechanical derivatives. This is especially a limitation in most studies, as the most striking feature of hypermobility related disorders is a high level of clinical heterogeneity in symptoms and connective tissue laxity and the migration of symptoms over specific joints over time that does not follow any predictable changes [16,17].

However, the literature does not provide a clear description of deviant gait features that are characteristic for JH, nor the consequences of these deviations for musculoskeletal complaints. Therefore, the objective of this exploratory study was to compare clinical features, biomechanical gait features (spatiotemporal data, kinetics and kinematics, joint impulse, ground reaction force and joint work) and gait variability between adolescents diagnosed with hEDS/HSD, those with JH and healthy controls.

2. Materials and methods

This cross-sectional study was conducted in adherence with the principles of the Declaration of Helsinki [21] and in accordance with the Human Subjects act (WMO). Ethical approval was granted by the Medical Ethical Committee of the Amsterdam University Medical Centre (Amsterdam UMC) (2015–040). The study was conducted at the Amsterdam UMC, location AMC, between January 2016 and December 2018.

2.1. Participants

Adolescents were eligible for participation when they were between 12 and 18 years of age. Adolescents were divided into three subgroups according to the 2017 classification criteria for Joint hypermobility and Ehlers Danlos syndromes [6,9]. The criteria for hEDS/HSD consist of three sub criteria, one of which is focused on joint hypermobility (Beighton score $\geq$6), sub criteria two is focused on various features (e.g. skin involvement and pain complaints) and sub criteria three consist of features associated with other heritable disorders such as rheumatological conditions. Adolescents with established hEDS or HSD according to the 2017 criteria [6,9] were recruited and included from the outpatient clinic of the Departments of Rehabilitation Medicine and Medical Genetics from the Amsterdam UMC. A group of adolescents was also recruited through members of the research team. The adolescents with asymptomatic joint hypermobility including asymptomatic generalized JH, asymptomatic peripheral JH and asymptomatic localized JH [6] and with mild to no complaints were classified as the joint hypermobile (JH-group) [6,9]. The remaining controls were classified as healthy controls (HC-group). Participants were excluded in case of presence or suspicion of HCTDs other than hEDS, recent surgery of the lower extremity or any other condition that might interfere with walking.

2.2. Demographics

Demographic data including age, sex, weight and body mass index (BMI) were collected.

2.2.1. Pain

Painful body surface area and number of pain locations were quantified by marking these on a pain manikin. The pain manikin consists of two body outlines, front and back, on which participants were asked to shade the body parts where they experienced pain for longer than the previous 24 h. The shaded area's provided a total percentage of painful body surface area [22]. In addition, A Visual Analogue Scale (VAS) was used to assess pain severity [23], as measured on a 0–100 scale ranging from 0 (no pain) to 100 (worst possible pain). The VAS has been demonstrated to have adequate psychometric properties [22,24].

2.2.2. Fatigue

Fatigue was measured with the multidimensional Checklist Individual Strength questionnaire (CIS20) [25]. The checklist consists of 20 items with a 7-points Likert scale scoring. Total scores are calculated through a summation of all subscales scores resulting in a score ranging from 20 to 140, with higher scores reflecting higher levels of fatigue and concentration problems and lower motivation and physical activity [25]. The CIS20 has shown to have good internal consistency, reliability and discriminative validity [25–28].

2.2.3. Functional disability

Functional disability and independence in daily life was measured with the Child Health Assessment Questionnaire (CHAQ-30). The 30 items of the self-administrated disability index assess eight domains of physical function with a 4-point Likert scale (0 =able to do with no difficulty; 3 =unable to do). The use of walking aids or assistance raised the score for that domain to at least 2 [29]. A higher score indicates more functional disability. The CHAQ has shown to have high reliability, validity and responsiveness to change over time [29–32].

2.2.4. Joint hypermobility

The Beighton score [33] was used for assessing generalized joint hypermobility [6,34] and consists of five tests including four bilateral tests (first finger opposition, fifth finger extension, elbow extension, knee extension) and forward bending. A score is obtained for each item (0 =negative or 1 =positive) per side, with a total score ranging from 0 to 9. A higher score indicates more joint hypermobility. The Beighton

score is found to be a high reliable clinical tool for measuring joint hypermobility [35].

2.2.5. Biomechanical gait features

Gait analysis of level overground walking was performed using a 3D 8-camera (100 Hz) Vicon MX 1.3 system (VICON, Oxford, UK), and two force plates (1000 Hz) in series (OR6–7, AMTI, Watertown, MA, USA). Anthropometric measures required by the Nexus software (version 1.4.116) were obtained, and reflective 14 mm passive body markers were placed on anatomical landmarks to fit the Plug-in-Gait model used. Participants were asked to walk barefoot at their own comfortable speed along a 12-meter walkway. Five valid trials were collected, in which (i) each foot landed individually on a force plate without targeting, and (ii) all markers were visible from first heel strike on the force plate to subsequent ipsilateral heel strike [36]. Trials were processed with standard Plug-In-Gait pipelines (VICON Nexus 1.8.5, Oxford, UK) [37] to obtain joint kinematics and kinetics and then time-normalized with spline interpolation and averaged, using a custom written Matlab script (version R2014a, The MathWorks, Inc., Natick, MA, U.S.A.). Gait analysis was focused on the loading response ([LR] 0–10% of the gait cycle) and terminal stance ([TS] 30–50% of the gait cycle) phase of the gait cycle according to Perry et al. [38].

2.2.5.1. Spatiotemporal characteristics. Average data for spatiotemporal characteristics (e.g. gait speed, step length and frequency), joint kinematics and kinetics and ground reaction forces were processed with Vicon Nexus software (version 1.4.116).

2.2.5.2. Kinematics. The output angles for all joints are calculated from the YXZ Cardan angles. The angles are derived by comparing the relative positionings of the segments proximal (parent) and distal (child) to the joint [37]. Based on previous conducted studies and clinical expertise the maximal ankle angle (dorsiflexion) and knee angle (flexion) during LR and the minimal knee angle during TS (knee extension) were assessed [18,39–41].

2.2.5.3. Kinetics. The kinetic models apply masses and moments of inertia to the segments, and then calculate the "reactions" that occur on the segments. The axis in the proximal segment embedded co-ordinate system about which each of the rotations take place given the Euler specifications per joint: ankle (-Y^1-Z-X), knee (YXZ) and hip (-YXZ) [37].

Joint impulse represents the force exerted on the joint or biomechanical strain during gait and was calculated over the complete lower extremity as a single entity (through summation of individual joint impulses using the area under the joint moment curve), and expressed in Nms/kg. Joint work in the complete lower extremity was assessed by calculating the area under the joint power curve, and expressed in J/kg [42]. The ground reaction force impulse (GRF-impulse, i.e. the area under the vertical GRF curve, not time-normalized) [43] was calculated to determine the loading, and expressed in Ns/kg.

2.3. Gait variability

Gait variability was assessed as a means to quantify motor control during gait for which Principle Component Analysis (PCA) was used [44]. Gait variability was expressed as the explained variance of the first two PCA components over five walking trials (full gait cycle). The PCA components were based on joint angle data (frontal, transverse and sagittal plane) for each individual joint (ankle, knee, hip) and total lower extremity (i.e. all three joints together).

2.4. Statistical analysis

For all collected data, normality assumptions were determined and non-parametric statistics were used in case of violation. Descriptive data were reported as mean and standard deviation (SD) if normally distributed, otherwise in median and interquartile range (IQR, 25th-75th).

To explore differences in demographics, pain, fatigue and functional disability between three subgroups (1 hEDS/HSD-group, 2 JH-group, 3 HC-group) the One-Way ANOVA or the Kruskal Wallis test was used. PCA analysis with varimax rotation (orthogonal) was performed to determine inter subject variability [44] in ankle, knee, hip and total lower extremity during gait and expressed in mean explained variance (%), Standard Errors (SE) and 95% Confidence Intervals (95%CI). Sampling adequacy was assessed by Kaiser-Meyer-Olkin measure (KMO). Adequate sampling was achieved when KMO $>$ 0.5. Factor loadings of $<$ 0.40 were suppressed.

To identify biomechanical gait features (spatiotemporal characteristics, kinetics and kinematics joint impulse, GRF-Impulse, joint work) and gait variability that discriminate between subgroups multivariate analysis was performed using Generalized Estimating Equation (GEE) [45]. Random effect models were constructed and corrected for gait speed (confounder(fixed)) and other potential confounders. Potential confounders were identified as a p-value of $<$ 0.200 for subgroups differences on sex, age weight and BMI. Mean group values were presented using mean or mean differences (MD), SE and 95%CI. A p-value of $<$ 0.05 was considered statistically significant. All analyses were performed in SPSS version 26.

3. Results

Thirty-two participants were included in the study (hEDS/HSD-group n = 12, hEDS/HSD-group n = 5, JH-group n = 15).

3.1. Demographics, pain, fatigue, functional disability, joint hypermobility

The hEDS/HSD-group had significantly higher Beighton scores (+3 points, p = <0.001), pain intensity (+38 mm, p = <0.001), levels of fatigue (+51.5 points, p = <0.001) and greater painful body surface (+29.7%, p = <0.001) and disability (+1.6 points, p = <0.001) compared to HC-group (Table 1). The hEDS/HSD-group showed a significantly higher pain intensity (+37 mm, p = <0.004, p = <0.001) compared to the JH-group.

3.1.1. Confounder analysis

None of the anthropometric measures were identified as potential confounder.

3.2. Multivariate analysis of biomechanical gait features and gait variability

The JH-group showed significantly increased ankle dorsiflexion during TS (MD(SE): + 5.0(1.5)degree, 95%CI: − 8.0 − −2.0, p = .001) compared to the hEDS/HSD-group, while knee flexion during LR was significantly increased compared to HC-group.

(MD(SE): + 5.7(1.8)degree, 95%CI: − 9.4 − −2.0, p = .011) (Table 2, Figs. 1 and 2). The hEDS/HSD-group had significantly lower total joint work compared to the JH-group (MD(SE)= −0.07(0.03)J/Kg, 95%CI= −0.12 − 0.02, p = .007) and HC-group (MD(SE)= −0.06(0.03) J/Kg, 95%CI= −0.07 − −0.04, p = .013) (Table 2, Figs. 1 and 2). The hEDS/HSD-group had significantly increased variability in ankle (MD (SE) = −9.2(1.8)%, 95%CI= −13.8 − −4.6, −p = <0.001), knee (MD (SE) = −5.2(2.1)%, 95%CI= −10.8 − −0.27, p = .037), hip (MD(SE) = −8.9(3.0)%, 95%CI= −16.5 − −1.4, p = .016) and lower limb (MD (SE)= −7.8(1.4)%, 95%CI= −11.5 − −4.3, p = <0.001) compared to the HC-group. Compared to the JH-group, the hEDS/HSD-group had significantly increased variability in hip (MD(SE)= −11.4(4.1)%, 95% CI= −21.8 − −1.0, p = .028) and lower limb (MD(SE) = −7.2(2.0)%, 95%CI= −12.2 − −2.2, p = <0.003) (Fig. 3).

Table 1
Comparison of demographics, pain, fatigue, functional disability, joint hypermobility between the hEDS/HSD, JH and HC groups.

hEDS/HSD		JH	HC	p-value
Number, N	12	5	15	
Sex, N (%)				
Female	10 (83.3)	4 (80)	7 (46.7)	0.112
Male	2 (16.7)	1 (20)	8 (53.3)	
Age years, median (IQR)	14.5 (13.3–17.0)	16.0 (13–17.5)	15.0 (14.0–17.0)	0.892
Weight kg, mean (SD)	55.0 (13.5)	56.6 (12.3)	62.0 (14.2)	0.403
BMI, mean (SD)	20.1(3.7)	19.5 (2.5)	20.8 (3.7)	0.772
Beighton score, median (IQR)	5.0 (4.0–6.0)	4.0 (4.0–5.0)	2.0 (0.0–3.0)	< 0.001[#]
VAS Pain intensity, mean (SD)	59.1 (20.5)	22.0 (19.8)	21.2 (20.2)	< 0.001[*,#]
Manikin painful body surface, median (IQR)	25.0 (21.2–45.5)	8.5 (5.8–21.3)	3.5 (0–5.0)	< 0.001[#]
CIS 20 Fatigue, median (IQR)	83.5 (75.2–91.0)	65.0 (39.5–86.0)	32.0 (22.0–54.0)	< 0.001[#]
CHAQ 30 Disability index, median (IQR)	1.6 (1.0–2.5)	0.13 (0.0–1.9)	0.0 (0.0-0.0)	< 0.001[#]

hEDS/HSD: Hypermobile Ehlers Danlos syndrome and Hypermobility spectrum disorders, participants with a confirmed diagnosis. JH= joint hypermobile group, HC=healthy controls, BMI=Body mass index, CIS=Checklist Individual Strength questionnaire, CHAQ=Child Health Assessment Questionnaire, VAS=visual analogue scale, Bold printed P-value represent significant differences between three groups using the One-way ANOVA or, in case of violation of the normality assumption, the Kruskal Wallis test. ‡=significant difference between JH-group and HC-group.
[*] =significant difference between hEDS/HSD-group and JH-group.
[#] =significant difference between hEDS/HSD-group and HC-group.

4. Discussion

The objective of this exploratory study was to identify discriminative clinical and biomechanical gait features between adolescents with hEDS/HSD, JH and HC. Adolescents with hEDS/HSD experienced significantly more pain and disability compared to HC. Variability and lower joint work during gait were discriminative for adolescents with hEDS/HSD.

Our observations are in line with previous studies in which no clear differences in gait biomechanics or gait pattern were observed between adolescents with JH and hEDS/HSD [18,46,47]. The only consistent unique aspect of gait that was deviant in our adolescents with hEDS/HSD was a higher gait variability compared to the JH-group and HC-group. However, the absence of clear biomechanical abnormalities in hEDS/HSD were in contrast with the general opinion that due to connective tissue laxity, gait abnormalities are present in adolescents with hEDS/HSD, which in turn may lead to joint damage and pain [23,48]. Nevertheless, the observations of more gait variability and lower joint work may indicate that the impact of hEDS/HSD is more of a contingent nature and the lack of stability is actively compensated with various strategies and high intra-individual variation [44]. Each individual seems to apply a unique strategy in gait, based on individual underlying features, such as limiting or increasing the degrees of freedom in various joints, as compensation, resulting in a more variable gait pattern. These observation may not infer causality and should only be viewed as exploratory but do illustrate the importance revisiting the general accepted assumption that local joint dysfunctions cause the accumulation of joint damage, and thus pain. As the only consistent observation was found the coordinative aspects of gait, a more complex mechanism in which neurological processes in the central nervous system (CNS) that is involved in the coordination of gait should be considered. However this suggestion, which also proposed by other authors [18–20,39], is an hypothesis that should warrant further scientific exploration. Especially when considering that joint stability is often considered as a target for treatment and other more systematic observations that the observed treatment effects of such approaches are highly variable and for some not effective. Gaining a better understanding on these mechanisms may prove to be vital for future treatment. The observations in this study should be viewed as observational, but does suggest that the origin of pain or the persistence may be far more complex than merely local biomechanical defects.

Recently, the first longitudinal observation in children with hEDS/HSD [49] showed that joint instability is an important determinant of disability and instability and is interconnected with other musculoskeletal deficits like pain and fatigue. Joint instability, combined with impaired proprioceptive in acuity, could provide an explanation for the

Table 2
Biomechanical gait features, comparison between hEDS/HSD, JH and HC groups.

	hEDS/HSD Mean (SE)	95%CI		JH Mean (SE)	95%CI		HC Mean (SE)	95%CI		P- value
		Lower	Upper		Lower	Upper		Lower	Upper	
Spatiotemporal parameters										
Gait speed, m/s	1.3 (0.05)	1.2	1.4	1.4 (0.09)	1.2	1.7	1.3 (0.05)	1.2	1.4	0.734
Cadence, steps/minute	118.7 (1.3)	116.0	121.4	114.5 (3.1)	108.6	120.8	116.4 (1.5)	113.4	119.4	0.346
Stride length, m	1.4 (0.02)	1.3	1.4	1.4 (0.04)	1.3	1.5	1.4 (0.02)	1.3	1.4	0.661
Step length, m	0.68 (0.01)	0.66	0.70	0.70 (0.02)	0.67	0.74	0.70 (0.01)	0.68	0.71	0.294
Kinetics and kinematics										
Ankle angle max TS	9.1 (1.0)	7.1	11.2	14.2 (1.1)	11.9	16.4	11.8 (1.0)	9.8	13.7	0.005[*]
Knee angle max LR	16.1 (1.42)	13.3	18.9	19.9 (1.42)	17.1	22.7	14.1 (1.1)	11.9	16.4	0.010[‡]
Knee angle min TS	-1.6 (1.1)	-3.8	0.54	2.6 (2.1)	-1.5	6.7	0.04 (0.92)	-1.8	1.9	0.176
Joint Impulse										
Lower limb impulse, Nms/kg	0.68 (0.01)	0.66	0.70	0.70 (0.02)	0.67	0.74	0.70 (0.01)	0.67	0.72	0.294
Joint work										
Lower limb joint work, J/kg	0.09 (0.02)	0.06	0.12	0.16 (0.02)	0.12	0.20	0.15 (0.02)	0.11	0.19	< 0.013[*,#]
Ground Reaction Force (GRF)										
Vertical GRF Impulse, Ns/kg	11.3 (0.31)	10.7	11.9	11.2 (0.21)	10.7	11.6	10.9 (0.23)	10.4	11.3	0.501

All parameters are corrected for gait speed using GEE modelling. hEDS/HSD: Hypermobile Ehlers Danlos syndrome and Hypermobility spectrum disorders, participants with a confirmed diagnosis, JH= joint hypermobile group, HC= healthy controls, SE= standard error, 95%CI= 95% confidence interval, min= minimum, max= maximum, knee angle max LR= maximum knee angle during loading response; values are knee flexion and negative values are knee extension, hip angle max MWS= maximum hip angle during midswing; positive values are hip flexion and negative values are hip extension, GRF=Ground reaction force. Bold printed P-value represent significant differences between three groups using GEE analysis.
[*] = significant difference between hEDS/HSD-group and JH-group.
[#] = significant difference between hEDS/HSD-group and HC group.
[‡] = significant difference between JH-group and HC-group.

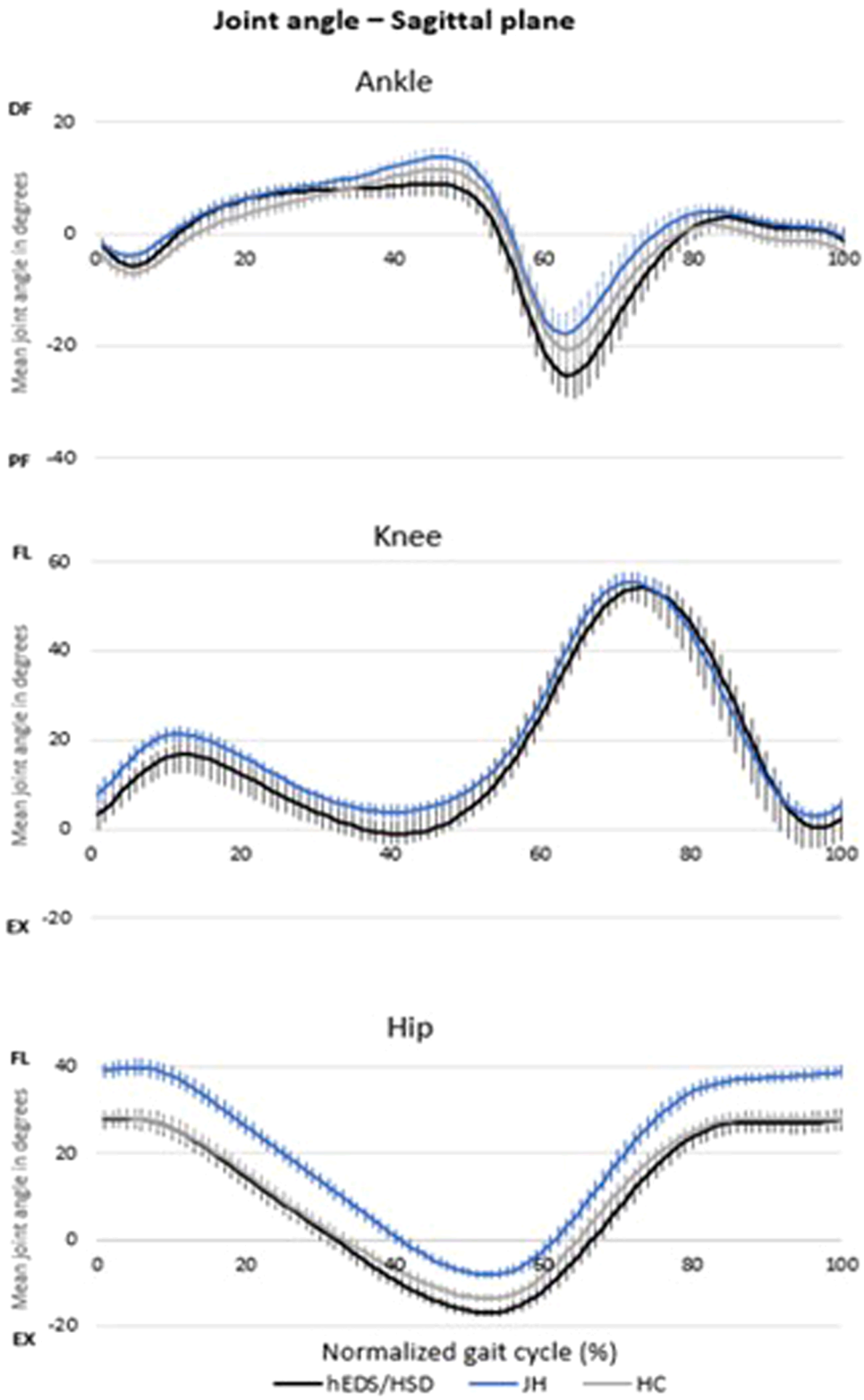

Fig. 1. Joint angles. Mean joint angles in degrees for three groups in sagittal plane for the right knee hip and ankle. DF=dorsal flexion, PF=plantar flexion, FL=flexion, EX=extension. Black lines: Children with Hypermobile Ehlers Danlos syndrome and Hypermobility spectrum disorders, confirmed diagnosis (hEDS/HSD), blue lines: children with joint hypermobility (JH), gray lines: healthy controls (HC). The vertical lines represent the standard deviation around the mean.

observed increased gait variability in the hEDS/HSD-group. Impaired motor control could in turn lead to biomechanical overload of individual joints and lead to the occurrence or persistence of joint pain. This might indicate that the origin of pain in hEDS/HSD could be more of an issue in motor control deficiency rather than being the result of connective tissue fragility. Generalized hyperalgesia, potentially originating from CNS hypersensitization, is present in adolescents and adults with hEDS/HSD [23]. The combination of an instable musculoskeletal system and hypersensitization of the CNS that is highly vulnerable for nociceptive information, could be a plausible hypothesis for the increase variability

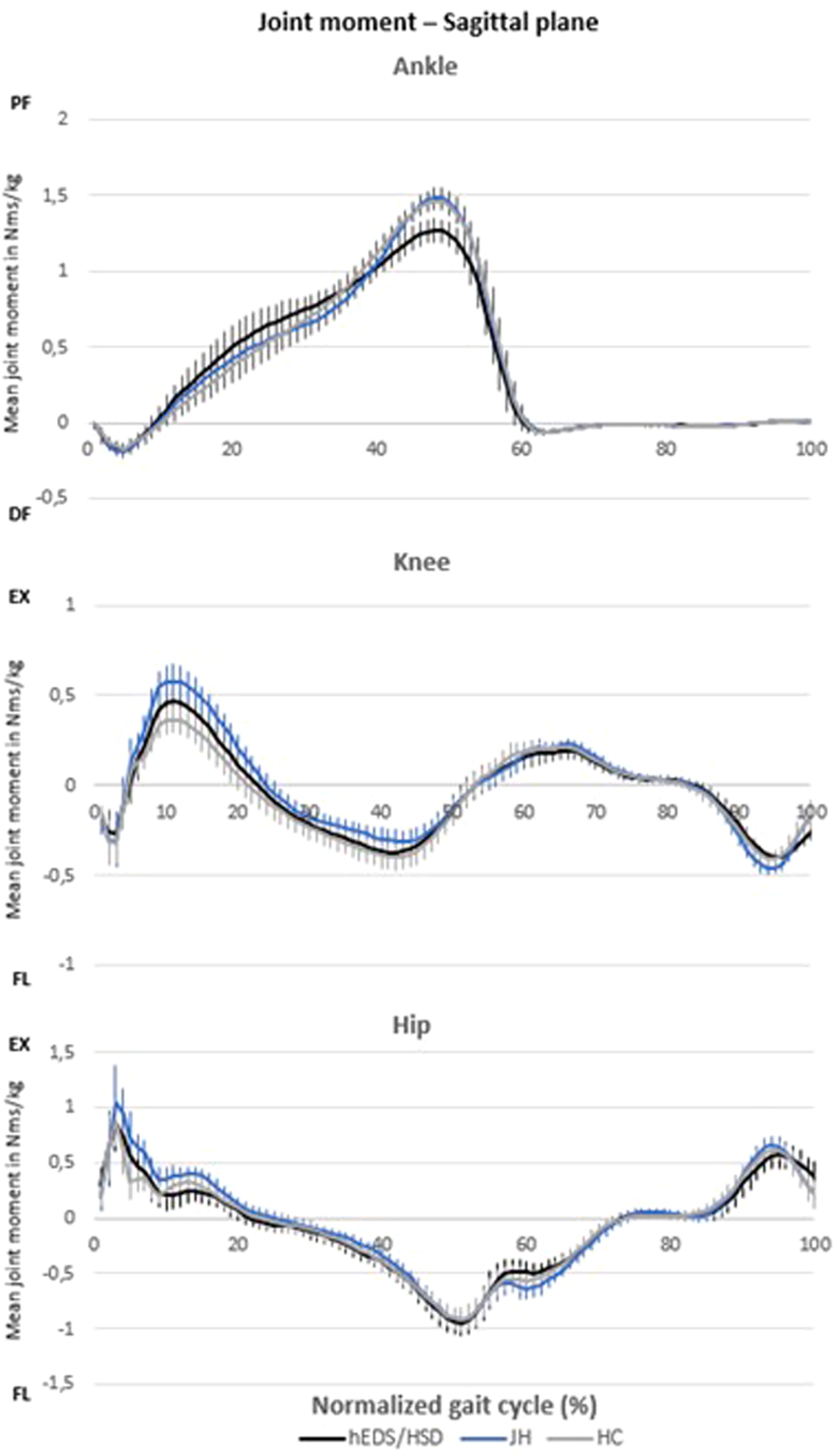

Fig. 2. Joint moments. Mean internal joint moments for three groups of children, in the sagittal plane for the right ankle, knee and hip during gait. Moments are normalized to kg (Nms/kg). DF=dorsal flexion, PF=plantar flexion, FL=flexion, EX=extension. Black lines: Children with Hypermobile Ehlers Danlos syndrome and Hypermobility spectrum disorders, confirmed diagnosis (hEDS/HSD), blue lines: children with joint hypermobility (JH), gray lines: healthy controls (HC). The vertical lines represent the standard deviation around the mean.

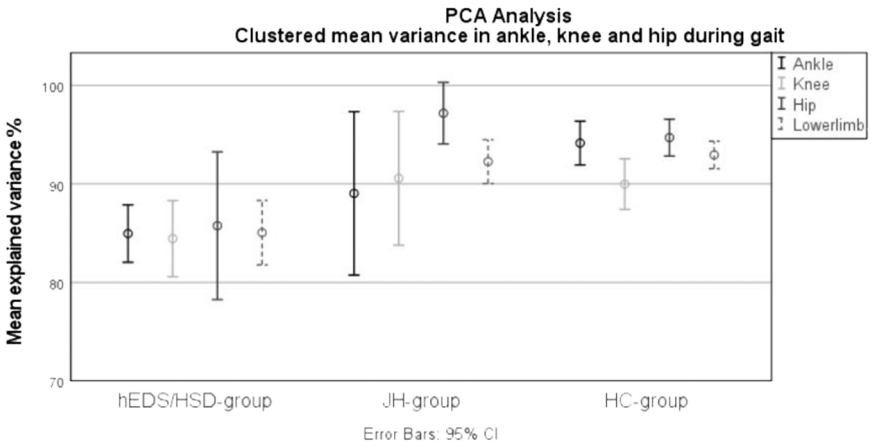

Fig. 3. Abbreviations: hEDS/HSD: Hypermobile Ehlers Danlos syndrome and Hypermobility spectrum disorders, participants with a confirmed diagnosis, JH= joint hypermobile group, HC= healthy controls, SE= standard error, 95%CI= 95% confidence interval, PCA= Principal Component Analysis.

in the hEDS/HSD-group, and may serve as an alternative theory for the biomechanical origins of pain in hEDS/HSD. The origin of pain is likely to develop based on multiple factors that combined and even possibly in several ways lead to disability without a single generalizable mechanism [23,48,49].

The following limitations of our study should be considered: (1) the biomechanics of gait in our study population is of an exploratory nature due to the small sample size, and uneven distribution of participants across subgroups, (2) the findings may provide an alternative view on the biomechanical origins of pain in hEDS/HSD and cannot infer causality due to the cross-sectional study design, (3) the observations suggest an impact of gait variability on pain whereas this should be studied more in-depth in prospective analyses, (4) no sample size calculation has been performed due to the fact that hEDS/HSD is a 'rare-condition'.

This alternative view on the biomechanical pathway in hEDS/HSD might have implications for clinical assessment and tailored interventions. The presence of gait variability suggests that the observation of gait in adolescents with hEDS/HSD should focus on the full chain of joints. For this, instrumented 3-D gait analysis may have limited application in clinical practice, as it is time-consuming, costly and often only available in academic settings. Therefore, for clinical practice, ways to assess gait variability based on the evaluation of gait using more straightforward clinical gait measures obtained using more observational gait assessment tools should be searched for.

5. Conclusions

This exploratory study examined clinical characteristics, biomechanical gait features and gait variability in adolescents with hEDS/HSD, JH and HC. Adolescents with hEDS/HSD experienced significantly more pain and disability compared to HC. Variability and lower joint work during gait were distinguishes features for adolescents with hEDS/HSD.

Our findings suggest that a specific gait variability metric is more appropriate than biomechanical individual joint patterns for assessing gait in adolescents with hEDS/HSD.

Role of funding sources

The funding sources did not have any role in the study design, the collection, analysis or interpretation of data.

Informed consent statement

Informed consent was obtained from all adolescents involved in the study.

Author contributions

L.E.d.K and M.C.S. conceptualized and designed the study, designed the data collection instruments, collected data, carried out the initial analysis, drafted the initial manuscript and revised the manuscript. H.E. P, J.W-K, J.O, S.A.B and R.H.H.E conceptualized and designed the study, designed the data collection instruments, reviewed and revised the manuscript.

Data Availability

All data are available from on request from the corresponding author.

Acknowledgements

The authors would like to acknowledge B. van Doornmalen, Dr. P. van Tintelen and the Dutch national support group for Ehlers-Danlos (VED) for their support in recruitment. In addtion, we would like to tank J. Croese for his contribution during the measurements. The authors would like to thank the adolescents and their families for their ongoing participation in this study.

Conflicts of Interest statement

The authors declare no conflict of interest.

References

[1] M. Mikkelsson, J.J. Salminen, H. Kautiainen, Joint hypermobility is not a contributing factor to musculoskeletal pain in pre-adolescents, J. Rheuma 23 (1996) 1963–1967.
[2] A. El-Metwally, J.J. Salminen, A. Auvinen, H. Kautiainen, M. Mikkelsson, Prognosis of non-specific musculoskeletal pain in preadolescents: a prospective 4-year follow-up study till adolescence, Pain 110 (2004) 550–559, https://doi.org/10.1016/j.pain.2004.03.021.
[3] L. Remvig, C. Kümmel, J.H. Kristensen, G. Boas, B. Juul-Kristensen, Prevalence of generalized joint hypermobility, arthralgia and motor competence in 10-yearold school children, Int Musculoskelet. Med 33 (2011) 137–145, https://doi.org/10.1179/1753615411Y.0000000009.
[4] B. Juul-Kristensen, J.H. Kristensen, B. Frausing, D.V. Jensen, H. Røgind, L. Remvig, Motor competence and physical activity in 8-year-old school children with generalized joint hypermobility, Pediatrics 124 (2009) 1380–1387, https://doi.org/10.1542/peds.2009-0294.
[5] R. Grahame, Joint hypermobility and genetic collagen disorders: are they related? Arch. Dis. Child 80 (1999) 188–191, https://doi.org/10.1136/adc.80.2.188.
[6] M. Castori, B. Tinkle, H. Levy, R. Grahame, F. Malfait, A. Hakim, A framework for the classification of joint hypermobility and related conditions, Am. J. Med Genet C. Semin Med Genet 175 (2017) 148–157, https://doi.org/10.1002/ajmg.c.31539.

[7] Baraitser, W.R.M. Michael. London Dysmorphology Database, London Neurogenetics Database & Dysmorphology Photo Library on CD-ROM, 3rd ed..,, Oxford University Press,, Oxford, 2001.

[8] C. Baeza-Velasco, M.C. Gély-Nargeot, G. Pailhez, A.B. Vilarrasa, Joint hypermobility and sport: a review of advantages and disadvantages, Curr. Sports Med Rep. 12 (2013) 291–295, https://doi.org/10.1249/JSR.0b013e3182a4b933.

[9] F. Malfait, C. Francomano, P. Byers, J. Belmont, B. Berglund, J. Black, et al., The 2017 international classification of the Ehlers-Danlos syndromes, Am. J. Med Genet C. Semin Med Genet 175 (2017) 8–26, https://doi.org/10.1002/ajmg.c.31552.

[10] N. Adib, K. Davies, R. Grahame, P. Woo, K.J. Murray, Joint hypermobility syndrome in childhood. A not so benign multisystem disorder? Rheumatology 44 (2005) 744–750, https://doi.org/10.1093/rheumatology/keh557.

[11] R. Grahame, The hypermobility syndrome, Ann. Rheum. Dis. 49 (1990) 199–200, https://doi.org/10.1136/ard.49.3.199.

[12] R. Grahame, Hypermobility - not a circus act, Int J. Clin. Pr. 54 (2000) 314–315.

[13] B. Tinkle, M. Castori, B. Berglund, H. Cohen, R. Grahame, H. Kazkaz, et al., Hypermobile Ehlers-Danlos syndrome (a.k.a. Ehlers-Danlos syndrome Type III and Ehlers-Danlos syndrome hypermobility type): clinical description and natural history, Am. J. Med Genet C. Semin Med Genet 175 (2017) 48–69, https://doi.org/10.1002/ajmg.c.31538.

[14] E. Crawley, Pediatric chronic fatigue syndrome: current perspectives, Pediatr. Health Med Ther. 9 (2017) 27–33, https://doi.org/10.2147/PHMT.S126253.

[15] N.C. Voermans, H. Knoop, N. van de Kamp, B.C. Hamel, G. Bleijenberg, B.G. van Engelen, Fatigue is a frequent and clinically relevant problem in ehlers-danlos syndrome, Semin Arthritis Rheum. 40 (2010) 267–274, https://doi.org/10.1016/j.semarthrit.2009.08.003.

[16] N.C. Voermans, H. Knoop, G. Bleijenberg, B.G. van Engelen, Fatigue is associated with muscle weakness in Ehlers-Danlos syndrome: an explorative study, Physiotherapy 97 (2011) 170–174, https://doi.org/10.1016/j.physio.2010.06.001.

[17] N.C. Voermans, H. Knoop, Both pain and fatigue are important possible determinants of disability in patients with the Ehlers-Danlos syndrome hypermobility type, Disabil. Rehabil. 33 (2011) 706–707, https://doi.org/10.3109/09638288.2010.531373.

[18] C. Celletti, M. Galli, V. Cimolin, M. Castori, G. Albertini, F. Camerota, Relationship between fatigue and gait abnormality in Joint Hypermobility Syndrome/Ehlers-Danlos Syndrome Hypermobility type, Res Dev. Disabil. 33 (2012) 1914–1918, https://doi.org/10.1016/j.ridd.2012.06.018.

[19] M. Castori, S. Morlino, C. Celletti, G. Ghibellini, M. Bruschini, P. Grammatico, et al., Re-writing the natural history of pain and related symptoms in the joint hypermobility syndrome/Ehlers-Danlos syndrome, hypermobility type, Am. J. Med Genet A 161 (2013) 2989–3004, https://doi.org/10.1002/ajmg.a.36315.

[20] V. Pacey, L. Tofts, A. Wesley, F. Collins, D. Singh-Grewal, Joint hypermobility syndrome: a review for clinicians, J. Paediatr. Child Health 51 (2015) 373–380, https://doi.org/10.1111/jpc.12731.

[21] General Assembly of the World Medical Association, World medical association declaration of Helsinki: ethical principles for medical research involving human subjects, J. Am. Coll. Dent. 81 (2014) 14–18.

[22] R.B. Margolis, R.C. Tait, S.J. Krause, A rating system for use with patient pain drawings, Pain 24 (1986) 57–65, https://doi.org/10.1016/0304-3959(86)90026-6.

[23] M.C. Scheper, R.H.H. Engelbert, E.A.A. Rameckers, J. Verbunt, L. Remvig, B. Juul-Kristensen, Children with generalised joint hypermobility and musculoskeletal complaints: state of the art on diagnostics, clinical characteristics, and treatment, Biomed. Res Int 2013 (2013), 121054, https://doi.org/10.1155/2013/121054.

[24] A. MCarlsson, Assessment of chronic pain. I. Aspects of the reliability and validity of the visual analogue scale, Pain 16 (1983) 87–101.

[25] J.H. Vercoulen, C.M. Swanink, J.F. Fennis, J.M. Galama, J.W. van der Meer, G. Bleijenberg, Dimensional assessment of chronic fatigue syndrome, J. Psychosom. Res 38 (1994) 383–392, https://doi.org/10.1016/0022-3999(94)90099-x.

[26] J.H. Vercoulen, C.M. Swanink, J.F. Fennis, J.M. Galama, J.W. van der Meer, G. Bleijenberg, Prognosis in chronic fatigue syndrome: a prospective study on the natural course, J. Neurol. Neurosurg. Psychiatry 60 (1996) 489–494, https://doi.org/10.1136/jnnp.60.5.489.

[27] J.H. Vercoulen, C.M. Swanink, F.G. Zitman, S.G. Vreden, M.P. Hoofs, J.F. Fennis, et al., Randomised, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome, Lancet 347 (1996) 858–861, https://doi.org/10.1016/s0140-6736(96)91345-8.

[28] J.W. Varni, T.M. Burwinkle, I.S. Szer, The PedsQL Multidimensional Fatigue Scale in pediatric rheumatology: reliability and validity, J. Rheuma 31 (2004) 2494–2500.

[29] T. Takken, F. Van Den Eijkhof, H. Hoijtink, P.J.M. Helders, J. Van Der Net, Examining the psychometric characteristics of the Dutch childhood health assessment questionnaire: Room for improvement? Rheuma Int 26 (2006) 979–983, https://doi.org/10.1007/s00296-006-0108-5.

[30] C. Lam, N. Young, J. Marwaha, M. McLimont, B.M. Feldman, Revised versions of the childhood health assessment questionnaire (CHAQ) are more sensitive and suffer less from a ceiling effect, Arthritis Care Res. (2004), https://doi.org/10.1002/art.20820.

[31] G. Singh, B.H. Athreya, J.F. Fries, D.P. Goldsmith, Measurement of health status in children with juvenile rheumatoid arthritis, Arthritis Rheum. (1994), https://doi.org/10.1002/art.1780371209.

[32] N. Wulffraat, J.J. van der Net, N. Ruperto, S. Kamphuis, B.J. Prakken, R. ten Cate, et al., The Dutch version of the childhood health assessment questionnaire (CHAQ) and the child health questionnaire (CHQ), Clin. Exp. Rheuma (2001) S111–S115.

[33] P. Beighton, L. Solomon, C.L. Soskolne, Articular mobility in an African population, Ann. Rheum. Dis. 32 (1973) 413–418, https://doi.org/10.1136/ard.32.5.413.

[34] B. Juul-Kristensen, K. Schmedling, L. Rombaut, H. Lund, R.H.H. Engelbert, Measurement properties of clinical assessment methods for classifying generalized joint hypermobility-a systematic review, Am. J. Med Genet C. Semin Med Genet 175 (2017) 116–147, https://doi.org/10.1002/ajmg.c.31540.

[35] L.N. Bockhorn, A.M. Vera, D. Dong, D.A. Delgado, K.E. Varner, J.D. Harris, Interrater and intrarater reliability of the beighton score: a systematic review, Orthop. J. Sports Med 9 (2021), https://doi.org/10.1177/2325967120968099.

[36] H.E. Ploeger, S.A. Bus, M.A. Brehm, F. Nollet, Ankle-foot orthoses that restrict dorsiflexion improve walking in polio survivors with calf muscle weakness, Gait Posture 40 (2014) 391–398, https://doi.org/10.1016/j.gaitpost.2014.05.016.

[37] Vicon Motion Systems Limited. Plug-inGait: ProductGuide—1.8.5 n.d. ⟨https://documentation.vicon.com/nexus/v2.2/Nexus1_8Guide.pdf⟩.

[38] J. Perry, J.M. Burnfield. Gait analysis. Normal and Pathological Function, second ed., Slack, California, 2010.

[39] F.A. Fatoye, S. Palmer, M.L. van der Linden, P.J. Rowe, F. Macmillan, Gait kinematics and passive knee joint range of motion in children with hypermobility syndrome, Gait Posture 33 (2011) 447–451, https://doi.org/10.1016/j.gaitpost.2010.12.022.

[40] H. Nikolajsen, P.K. Larsen, E.B. Simonsen, T. Alkjær, S. Falkerslev, J.H. Kristensen, et al., Gait pattern in 9-11-year-old children with generalized joint hypermobility compared with controls; a cross-sectional study, BMC Musculoskelet. Disord. 14 (2013) 341, https://doi.org/10.1186/1471-2474-14-341.

[41] Galli M., Cimolin V., Rigoldi C., Castori M., Celletti C., Albertini G., et al. Gait strategy in patients with Ehlers-Danlos syndrome hypermobility type: a kinematic and kinetic evaluation using 3D gait analysis. Res Dev Disabil n.d.;32:1663–8. ⟨https://doi.org/10.1016/j.ridd.2011.02.018⟩.

[42] N.F.J. Waterval, M.A. Brehm, H.E. Ploeger, F. Nollet, J. Harlaar, Compensations in lower limb joint work during walking in response to unilateral calf muscle weakness, Gait Posture 66 (2018) 38–44, https://doi.org/10.1016/j.gaitpost.2018.08.016.

[43] J. Wu, T. Ajisafe, Kinetic patterns of treadmill walking in preadolescents with and without down syndrome, Gait Posture 39 (2014) 241–246, https://doi.org/10.1016/j.gaitpost.2013.07.113.

[44] A. Daffertshofer, C.J.C. Lamoth, O.G. Meijer, P.J. Beek, PCA in studying coordination and variability: a tutorial, Clin. Biomech. 19 (2004) 415–428, https://doi.org/10.1016/j.clinbiomech.2004.01.005.

[45] A.E. Hubbard, J. Ahern, N.L. Fleischer, M. Van der Laan, S.A. Lippman, N. Jewell, et al., To GEE or not to GEE: comparing population average and mixed models for estimating the associations between neighborhood risk factors and health, Epidemiology 21 (2010) 467–474, https://doi.org/10.1097/EDE.0b013e3181caeb90.

[46] H. Nikolajsen, P.K. Larsen, E.B. Simonsen, T. Alkjær, S. Falkerslev, J.H. Kristensen, et al., Gait pattern in 9-11-year-old children with generalized joint hypermobility compared with controls; a cross-sectional study, BMC Musculoskelet. Disord. 14 (2013), https://doi.org/10.1186/1471-2474-14-341.

[47] N. Alsiri, M. Cramp, S. Barnett, S. Palmer, Gait biomechanics in joint hypermobility syndrome: a spatiotemporal, kinematic and kinetic analysis, Musculoskelet. Care 18 (2020) 301–314, https://doi.org/10.1002/msc.1461.

[48] V. Pacey, L. Tofts, A. Wesley, F. Collins, D. Singh-Grewal, Joint hypermobility syndrome: a review for clinicians, J. Paediatr. Child Health 51 (2015) 373–380, https://doi.org/10.1111/jpc.12731.

[49] M.C. Scheper, L.L. Nicholson, R.D. Adams, L. Tofts, V. Pacey, The natural history of children with joint hypermobility syndrome and Ehlers-Danlos hypermobility type: a longitudinal cohort study, Rheumatol. (U. Kingd.) 56 (2017) 2073–2083, https://doi.org/10.1093/rheumatology/kex148.