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ORIGINAL ARTICLE

Are chronic musculoskeletal pain and generalized joint hypermobility disabling contributors to physical functioning?

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ABSTRACT

BACKGROUND: Chronic musculoskeletal pain (CMP), Generalized Joint Hypermobility (GJH) and pain-related fear have influence on physical functioning in adolescents.
AIM: to evaluate differences in physical functioning between adolescents with CMP, GJH or the combination of both, and in addition evaluate the potential contribution of pain-related fear.
DESIGN: The design of this study was observational and cross-sectional.
SETTING: The adolescents with CMP were recruited by a physician in rehabilitation medicine and measured in the university outpatient rehabilitation clinic (Adelante/Maastricht University Medical Center+, the Netherlands). The adolescents without CMP were recruited in the Southern area of the Netherlands and measured in the university outpatient rehabilitation clinic (Adelante/Maastricht University Medical Center+, the Netherlands).
POPULATION: Four subgroups of adolescents were included; 21 adolescents with CMP without GJH, 9 adolescents with CMP and GJH, 51 adolescents without CMP without GJH, and 11 adolescents without CMP with GJH.
METHODS: Outcome measures were muscle strength and endurance, motor performance, physical activity level, and pain-related fear. Hierarchical regression analyses were used to study differences in physical functioning and the contribution of pain-related fear in adolescents with/without CMP as well as with/without GJH.
RESULTS: Adolescents with CMP had decreased muscle strength (P=0.01), endurance (P=0.02), and lower motor performance (P<0.01) compared to adolescents without CMP. Higher levels of pain-related fear were related to decreased muscle strength (P=0.01), endurance (P<0.01), and motor performance (P<0.01). No differences in physical functioning and pain-related fear between hypermobile and non-hypermobile adolescents with CMP were found.
CONCLUSIONS: Adolescents with CMP had decreased muscle strength and motor performance associated with increased levels of pain-related fear compared to adolescents without CMP. The association of being hypermobile with physical functioning is not more pronounced in adolescents with CMP.
CLINICAL REHABILITATION IMPACT: No differences were found in physical functioning and pain-related fear between hypermobile adolescents with CMP compared to non-hypermobile adolescents with CMP. Future rehabilitation treatment in hypermobile adolescents with CMP should also focus on psychological components, such as pain-related fear.

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KEY WORDS: Activities of daily living; Chronic pain; Fear; Joint instability; Muscle strength.

Pain lasting for more than 3 months is referred to as chronic pain.[1] Chronic pain is a complex health issue in which physiological, psychological, and social factors contribute to the level of pain-related disability.[2] In the Netherlands, up to 25% of the schoolchildren report chronic pain, such as headache, abdominal pain or chronic musculoskeletal pain (CMP).[3] In CMP, often a specific medical disease cannot explain the level of disability, re-

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sulting in a non-specific condition based on the location of symptoms in the bones, joints, muscles or related soft tissues.[4] In approximately 40% of adolescents with CMP, pain has a considerable disabling impact on physical functioning (associated with deficits in motor performance, difficulty with balance or decreased muscle strength), mood, and social functioning, reducing the quality of life.[5, 6]

Previous studies suggest a relationship between CMP and Generalized Joint Hypermobility (GJH), as GJH has been reported as a two to threefold increased risk of developing CMP.[7, 8] GJH associated with one or more musculoskeletal manifestations such as chronic widespread pain for ≥3 months, macro- and microtrauma, disturbed proprioception, and joint instability, is referred to as Generalized Hypermobility Spectrum Disorder (G-HSD).[9] G-HSD shows close overlap with the hypermobile Ehlers-Danlos syndrome (hEDS).[10] Both symptomatic conditions lack a specific genetic profile, have been identified as clinically indistinguishable[11] and are therefore labelled as G-HSD/hEDS.

Common physical symptoms in children and adolescents with G-HSD/hEDS that have been reported are decreased muscle strength,[12] reduced cardiorespiratory fitness,[13] impaired proprioception,[12] and reduced balance.[14] Furthermore, children and adolescents reported decreased level of participation in activities.[14] Deconditioning has been reported as a potential underlying explanation for decreased functioning in musculoskeletal pain. According to the fear-avoidance model, musculoskeletal pain can be perceived as a threat, and pain-related fear can evolve causing avoidance behavior. This pain-related behavior might result in disuse, functional disability, and depression, resulting in deconditioning further fueling the vicious circle of CMP. Even more, individuals with G-HSD/hEDS have been found to report higher levels of pain-related fear[15, 16] and more generalized anxiety.[17] It is hypothesized that this vulnerability for heightened fear and anxiety might lead to further disabilities and thus a further decline in physical functioning. In earlier studies, it was found that adolescents with asymptomatic, thus pain-free, GJH have decreased functional capacity, expressed as a decrease in walking distance and jumping capacity,[18] decreased muscle strength,[19] and preferring more stable activities, such as walking and cycling.[19] Other studies could not confirm the altered physical activity level and reduced muscle strength in GJH.[20, 21]

Thus, it remains still unclear whether having CMP, being hypermobile in the joints, having the combination of both, or the contributing role of pain-related fear will have the most impact on physical functioning. Therefore, the main aim of this study was to evaluate the influence of GJH and having CMP on the level of physical functioning (measured as muscle strength, motor performance, and physical activity level [PAL]) in adolescents. We hypothesized that having CMP and GJH will negatively interact on physical functioning in adolescents than CMP alone. Furthermore, we want to examine the specific role of pain-related fear on physical functioning. We hypothesize that higher levels of pain-related fear in adolescents with G-HSD/hEDS are related to decreased levels of physical functioning compared to adolescents with CMP.

Materials and methods

Participants and procedure

In this cross-sectional study both adolescents with CMP and healthy adolescents participated. First, thirty adolescents (mean age 16.4 years; SD 1.7 years; range 13-20 years) with CMP and GJH (+/+) or with CMP and without GJH (+/-) were recruited by a physician in rehabilitation medicine in the university outpatient rehabilitation clinic specializing in pain rehabilitation (Adelante/Maastricht University Medical Center+, the Netherlands). Inclusion criteria were a treatment indication for outpatient rehabilitation treatment, considerable perceived disabilities in daily life functioning, and good understanding of the Dutch language. Exclusion criteria were any suspicion of a medical (orthopedic, rheumatic, neurological) disease that could fully explain their current level of pain, or any suspicion of an underlying psychiatric disorder that would hamper rehabilitation treatment. The adolescents with CMP were participants in the multicenter 2B-Active trial (NL47323.068.13), which was conducted in Adelante/Maastricht University Medical Center+, Laurentius Hospital Roermond, Revant Rehabilitation Center Breda, and Rijndam Rehabilitation Center in Rotterdam. Ethical approval was granted by the Medical Ethics Committee of the Academic Hospital Maastricht/Maastricht University, the Netherlands (METC; 13-3-062) in accordance with the principles set forth in the Helsinki Declaration in October 2013. The 2B-Active study investigated the effectiveness of a multidisciplinary rehabilitation treatment including exposure *in-vivo* treatment in reducing functional disability in adolescents with CMP compared with care as usual. Baseline measurements including physical functioning measurements were completed before the start of the outpatient rehabilitation treatment. On a single study site (Adelante/Maastricht University Medical Center+) baseline measurements also included assessment on physical func-

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tioning. Sample size calculation for the adolescents with CMP was based on the primary outcome measure of the multicenter trial, Functional Disability Inventory (FDI). A total of 124 participants was calculated, the full estimation is published elsewhere.[22] For study site Maastricht, 62 participants were anticipated for in 2B-Active.[23] Only 30 adolescents could eventually be included in the current study and a flow chart is published elsewhere.[22]

Second, anticipating on 62 adolescents with CMP to participate, also 62 healthy adolescents (mean age 16.8 years; SD 2.3 years; range 12-21 years) without CMP with GJH (-/+) or without CMP and without GJH (-/-) were recruited in the Southern area of the Netherlands. The inclusion of the adolescents without CMP with GJH (-/+) and without CMP and without GJH (-/-) was in the same time period to the adolescents with CMP and GJH (+/+) and with CMP and without GJH (+/-) (Figure 1). Therefore, the composition of the adolescent population without CMP was based on age and gender of the adolescents with CMP. Recruitment of these healthy adolescents was organized in three different ways: 1) informed on a local high school; 2) responded on a pamphlet presented at two institutes for higher education; and 3) asked in the personal network of the research group. Adolescents who were interested received an information letter and after a week, a researcher contacted them for participating in the study. Inclusion criteria were good understanding of the Dutch language and adolescents were excluded if there was a specific medical condition influencing physical functioning such as acute or recurrent musculoskeletal pain or a history of surgical interventions. Ethical approval was granted by the Medical Ethics Committee of the Academic Hospital Maastricht/Maastricht University, the Netherlands (METC; 15-4-052) in accordance with the principles set forth in the Helsinki Declaration in October 2013. All adolescents and, if younger than 18 years of age, also from their parents provided written informed consent.

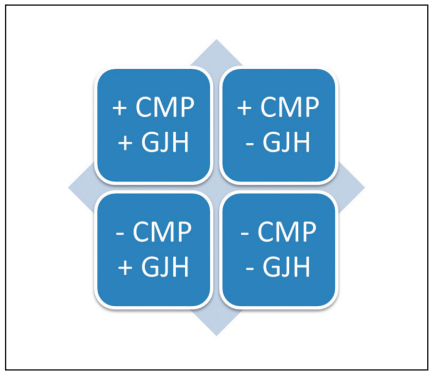

Figure 1.—Explaining the different groups. +CMP+GJH: adolescents with chronic musculoskeletal pain and generalized joint hypermobility; +CMP-GJH: adolescents with chronic musculoskeletal pain and no generalized joint hypermobility; -CMP+GJH: healthy adolescents with asymptomatic generalized joint hypermobility; -CMP-GJH: healthy adolescents without asymptomatic generalized joint hypermobility.

All outcome measures were collected by a physical therapist blinded for the condition during an 1-hour session. Assessment of the adolescents with CMP and with or without GJH were at baseline prior to the start of their outpatient rehabilitation treatment. Healthy adolescents without CMP and with or without GJH were invited to come to the hospital once in order to participate in the study assessment procedure.

Outcome measurements

Sociodemographic variables (age, gender) were collected. Height (meters; m) and weight (kilograms; kg) were measured in a standardized method without heavy clothing and shoes. Body Mass Index (BMI; kg/m^2) was calculated as weight divided by the square of height. Perceived difficulty in performing activities at school, at home, and in recreational or social interactions was assessed with the Functional Disability Inventory (FDI) in the adolescents with CMP. The FDI is a reliable and valid instrument to evaluate pain-related disability in adolescents.[24]

Hypermobility

The presence of joint hypermobility was assessed using Beighton score (BS), with a standardized protocol. The BS consist out of nine functional tests and scored dichotomously (0/1) with a maximum score of nine. The cut-off point for adolescents younger than 18 years is 6 out of 9 and the cut-off point for adolescents older than 18 years is 5 out of 9.[25] The BS is the most commonly used method in clinical practice.[25] In the adolescents with CMP, a physician in rehabilitation medicine measured GJH using BS. This protocol was also used by a physical therapist to measure GJH in the adolescents without CMP.

Physical functioning

In order to reflect various components of physical functioning: muscle strength, muscle strength endurance, motor performance, and physical activity in daily life (PAL) were assessed.

Muscle strength

For measuring isokinetic knee extensor and knee flexor muscle strength in both legs, a dynamometer (Biodex Sys-

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tem 3 Pro dynamometer; Biodex Medical Systems, Shirley, NY, USA) was used. Knee muscle strength is an important factor in balance and functional activities of daily living, such as standing up, stairs climbing, and gait.[26] The adolescents took place in an upright sitting position and the tested upper leg was stabilized with a fixation strap. The lever arm was attached to the adolescent's lower leg by a padded cuff 2 cm proximal to the medial malleolus. The axis of movement of the knee extension/flexion was in line with the axis of movement of the Biodex. After one practice repetition, five repetitions of maximal voluntary concentric knee extension and flexion were performed at the angular velocity of 60°/second. Peak torque/body weight (PT/BW) was used to standardize and interpret isokinetic muscle strength.

The same setup was used to measure isokinetic knee extensor and knee flexor muscle strength endurance in both legs. The adolescent had to perform 30 repetitions of maximal voluntary concentric knee extension and flexion with an angular velocity of 240°/second after one practice repetition. The test was performed 60 seconds after the isokinetic test of 60°/second. Total work (J) was used to represents the muscle's capacity. The Biodex is a valid and reliable isokinetic dynamometer in adolescents.[27]

Motor performance

For measuring motor performance related to balance, coordination, and joint stability, the single leg hop for distance (SLHD) was used.[28] The adolescents were asked to jump as far as possible on a single leg, without losing balance. After one practice hop, three valid hops with both legs were performed with a resting period of 30 seconds in between. The greatest distance (centimeters) from the toe at the push off to the heel at the place the adolescents landed was used for the analyses. The SLHD has shown high intra-subject reliability.[29]

Physical activity in daily life (PAL)

PAL during daily life was measured using a tri-axial accelerometer (AX3; Axivity, Newcastle, UK) attached to the waist using plaster (Tegaderm Film; 10×12 cm). The AX3 had to be removed during potential harmful activities for the device, such as swimming and contact sports. Each adolescent received a diary to collect information of wake up time, sleeping, and non-wearing time and the reason for doing this. To be included as a valid score, at least three weekdays with a minimum of 10 hours of recording and one weekend day with at least 8 hours of recording had to be available during a 7-day monitoring period.[30] To obtain activity counts an algorithm was designed using Matlab (The Math Works Inc., Natick, MA, USA), based on the method which was used for the Actiwatch 7 (Philips, Eindhoven, the Netherlands). The highest recorded sample per minute was selected and summed per minute. This counts/minute signal was used for all further calculations. Daily uptime (minutes) was defined as the period between wake up time and sleeping. PAL was expressed as total activity (TA) during uptime. This quantity was calculated as the total sum of counts during uptime averaged over the week.[31]

Pain intensity

Pain intensity was measured using a 100-mm visual analogue scale (VAS), ranging from 0 (no pain) to 100 (worst pain imaginable). The adolescents rated their pain intensity in three conditions: 1) current pain; 2) the worst/most severe pain experienced in the last week; and 3) the least pain experienced in the last week. The mean of these three VAS scores was used. The VAS is a reliable and valid measurement in children older than 8 years.[32]

Perceived harmfulness

Perceived harmfulness, as construct of pain-related fear, was measured with the Photograph Series of Daily Activities for youth (PHODA-youth). The PHODA-youth contains 51 age-specific activities and social situations and consists out of three categories: activities of daily living and household (PHODA-ADL; 13 items), intensive physical activities (PHODA-PA; 27 items) and social activities (PHODA-SA; 11 items). Adolescents rate the photographs from 0 ("not harmful at all") to 10 ("extremely harmful"), where higher scores indicated higher levels of perceived harmfulness. The PHODA-youth is valid and reliable in adolescents with CMP.[33]

Statistical analysis

Normality of the data and the presence of outliers was checked by visual assessment and the Kolgomorov-Smirnov goodness-of-fit test. Descriptive data of sociodemographic and anthropometric variables, hypermobility, functional disability (CMP group only), and pain intensity of the CMP group with/without GJH and the non-CMP with/without GJH were calculated. Normal distribution of data were presented as mean±standard deviation (SD), non-normal distribution data were presented as median and interquartile range (IQR). Categorical data were shown as frequencies.

In order to study differences in physical functioning and pain-related fear measured as perceived harmfulness

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in adolescents with both CMP and GJH, adolescents with CMP without GJH, adolescents without CMP with GJH, and those without CMP nor GJH multiple one-way ANOVA's were used in case of a normal distribution. In case of a significant result, a *post-hoc* Hochberg's GT2 analysis was performed to explore potential differences between groups. In case of non-normal distribution, the Kruskall-Wallis test was used. Subsequent multiple comparisons included Mann-Whitney U test. For the categorical variables, the Fisher's Exact test was used.

In order to evaluate the influence of having GJH and having CMP on the level of physical functioning (muscle strength, motor performance, and PAL) in adolescents, and to examine the specific role of pain-related fear on physical functioning, hierarchical regression analyses were performed. Variables were entered in three steps. In the first step, physical functioning (respectively expressed as muscle strength [1], muscle strength endurance [2], motor performance [3], and physical activity level [4]) were the dependent variables. In each model having CMP (no, 0; yes, 1), GJH (no, 0; yes, 1), age, and gender (male, 0; female, 1) were entered as independent variables. Age and gender were added to control for demographic variables. In the second step, pain-related fear (measured as perceived harmfulness) was introduced. In the third step, the interaction term (CMP*GJH) was entered. In case of a significant interaction (P<0.10), additional regression analyses were performed for the CMP group and the non-CMP group separately with the physical functioning outcome as dependent variable and GJH, age, gender, and pain-related fear as independent variables.

For all independent variables, the association with the outcome was presented by the regression coefficient (B), the corresponding 95% confidence interval (95%-CI), and P value. It appeared that knee extension and knee flexion muscle strength endurance did not meet the assumption of normality; these variables were log transformed prior to the analyses. After transformation, skewness and kurtosis values of the scales were in acceptable range of -1 and +1. For all regression analyses, a collinearity check was performed. Collinearity was considered a problem if the variance inflation factor (VIF) was above 10.[34] P values <0.05 were considered statistically significant. All statistical analyses were performed in IBM SPSS Statistics for Windows v23.0 (IBM Corp, Armonk, NY, USA).

Data availability statement

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Results

Description of the population

A total of 92 adolescents, 30 adolescents with CMP and 62 adolescents without CMP, participated in the present study. Within the CMP group 9 of 30 adolescents had GJH (30%) and within the non-CMP group 11 of 62 adolescents had GJH (18%). The characteristics of each group are presented in Table I. The mean score of the FDI was respectively 24.3±8.0 in the adolescents with CMP and without GJH (+/-) and 22.1±13.4 (not significant) in the adolescents with CMP and GJH (+/+), which is classified as moderate disability (score 13-29).[24] With respect to gender, age, height, weight, and BMI, no significant differences were found between the four groups (CMP without GJH (+/-), CMP with GJH (+/+), without CMP without GJH (-/-), and without CMP with GJH (-/+)). As expected, the Beighton score was significant higher (P<0.01) in the CMP with GJH and the non-CMP with GJH compared to the CMP without GJH

TABLE I.—*Characteristics of the study population of adolescents with and without CMP and with and without GJH.*

	CMP (N.=30)		No CMP (N.=62)		Test statistics
	No GJH (N.=21)	GJH (N.=9)	No GJH (N.=51)	GJH (N.=11)	
Female/male, N.	19/2	8/1	37/14	10/1	P=0.273
Age, y	16.1 (2.0)	16.9 (0.8)	16.5 (2.3)	18.1 (1.8)	F(3, 88)=2.36, P=0.08
Height, m	1.66 (0.08)	1.71 (0.03)	1.70 (0.09)	1.70 (0.10)	F(3, 88)=0.99, P=0.40
Weight, kg	60.5 (57.3-72.8)	80.4 (56.6-110.3)	59.0 (53.1-69.7)	63.1 (52.0-73.7)	H(3)=6.12, P=0.11
BMI, kg/m^2	22.1 (21.0-27.0)	27.6 (19.8-37.1)	21.5 (18.9-23.0)	22.1 (18.5-24.2)	H(3)=7,36, P=0.06
Beighton, n	2 (1-3) [a]	6 (6-7) [b]	2 (2-3) [a]	6 (5-7) [b]	H(3)=47.86, P<0.001
Pain intensity, mm	53 (38-77) [a]	68 (37-78) [a]	3 (0-11) [b]	5 (0-9) [b]	H(3)=51.66, P<0.001
Functional disability	24.3 (8.0) [c]	22.1 (13.4) [d]	-	-	t(25)=0.40, P=0.70

Normally distributed data are presented by means (SD) and not normally distributed data are presented by median (interquartile ranges; 25-75th percentile). Functional disability is only measured in the CMP population.
BMI=Body Mass Index.
[a, b]Values with the same superscripts represent homogenous subsets; [c]N.=20; [d]N.=7.

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and the non-CMP without GJH, and pain intensity was significant higher (P<0.01) in the CMP with and without GJH compared to the non-CMP with and without GJH.

Physical functioning and pain-related fear

One non-CMP adolescent without GJH could not complete the muscle strength endurance testing due to malfunction of the dynamometer. Three adolescents with CMP (2 with GJH and 1 without GJH) did not complete the PHODA-youth. For the assessment of PAL, accelerometry data of 76 adolescents (27 adolescents with CMP; 49 adolescents without CMP) was used. Data of 16 adolescents (3 adolescents with CMP; 13 adolescents without CMP) were excluded due to the following reasons: dysfunction of the accelerometer (N.=3), not fulfilling the predetermined criteria for a valid registration (N.=12), and interruption of the measurement due to an allergic reaction to the plaster (N.=1). Table II presents mean (SD) and median scores (IQR) on the four components of physical functioning and pain-related fear of the four subgroups. The subgroups CMP with/without GJH scored significantly higher on pain-related fear compared to non-CMP with/without GJH (P<0.01). No differences in pain-related fear was found between the CMP with GJH and the CMP without GJH (P=0.38).

Associations between having CMP and GJH, pain-related fear, and physical functioning

Muscle strength

Table III presents the results of the hierarchical regression analyses with muscle strength as dependent variable. The first step showed that older adolescents had increased knee extension muscle strength (B=7.58; P=0.01) and having CMP was associated with decreased knee flexion muscle strength (B=-22.88, P=0.01). In the second step, the PHODA-youth was associated with knee extensor (B=-0.24, P=0.01) and flexor (B=-0.17, P=0.01) muscle strength, indicating that higher perceived harmfulness was associated with decreased muscle strength. In the final step, the interaction term CMP*GJH was introduced. There was a significant association (P<0.10) with decreased knee extensor muscle strength (P=0.04) and knee flexor muscle strength (P=0.07). The analysis per subgroup (CMP group and non-CMP group) revealed that higher pain-related fear was associated with decreased knee extensor (B=-0.25, P=0.02; R^2=0.28) and flexor muscle strength (B=-0.15, P=0.01; R^2=0.33) in adolescents with CMP. No significant association was found for having GJH in the CMP group (muscle strength extension: B=-19.60, P=0.48; muscle strength flexion: B=-20.74, P=0.19). In the non-CMP group having GJH (B=41.05, P=0.03) was associated with increased knee extensor muscle strength (corresponding R^2=0.21).

Muscle strength endurance

For muscle strength endurance the first step showed that having CMP was associated with decreased knee extension (B=-0.20; P=0.02) and decreased knee flexion (B=-0.20; P<0.01). Furthermore, a higher age was associated with increased knee extension (B=0.04; P=0.04) and increased knee flexion (B=0.03, P=0.05) muscle strength endurance. After adding perceived harmfulness in step 2, significant associations were found with knee extension (B<-0.01, P<0.01) and knee flexion (B<-0.01, P<0.01) muscle strength endurance. In the final step, the interaction term CMP*GJH was not significantly associated with knee extensor and knee flexor muscle strength endurance (Table III).

TABLE II.—*Characteristics of all physical outcomes and pain-related fear from adolescents with and without CMP and with and without GJH.*

	CMP (N.=30)		No CMP (N.=62)		Test statistics
	No GJH (N.=21)	GJH (N.=9)	No GJH (N.=51)	GJH (N.=11)	
Muscle strength extension (PT/BW)	108.9 (61.9)[a]	81.2 (65.6)[a]	118.3 (53.3) [a]	170.2 (51.3)[b]	F(3, 88)=4.61, P=0.01
Muscle strength flexion (PT/BW)	80.1 (36.0)[a, b]	55.8 (38.4)[a]	93.2 (37.1)[b]	110.9 (32.2)[b]	F(3, 88)=4.45, P=0.01
Muscle strength endurance extension (TW)	560.9 (283.3-1074.5)[a]	310.2 (156.0-1178.0)[a]	774.1 (353.5-1193.1) [a, b; N.=50]	1594.7 (628.4-1698.4)[b]	H(3)=9.63, P=0.02
Muscle strength endurance flexion (TW)	573.5 (292.9-991.3)[a]	367.7 (190.5-1194.1)[a, b]	922.2 (397.6-1302.9)[b; N.=50]	1238.8 (707.6-1437.7)[b]	H(3)=9.05, P=0.03
Motor performance	108.7 (42.2)[a]	97.6 (28.2)[a]	149.6 (29.1)[b]	145.9 (23.3)[b]	F(3, 88)=12.83, P<0.01
Physical activity level (PAL)	1.7×10^5 (0.6×10^5)	1.6×10^5 (0.4×10^5) [N.=18]	1.6×10^5 (0.5×10^5) [N.=41]	1.7×10^5 (0.3×10^5) [N.=8]	F(3,72)=0.50, P=0.69
Pain-related fear	168.9 (70.2-253.8) [a; N.=20]	249.7 (122.7-304.0) [a; N.=7]	8.0 (1.0-38.0)[b]	5.0 (2.0 - 16.5)[b]	H(3)=39.51, P<0.01

Normally distributed data are represented by means (SD) and not normally distributed data are represented by medians (interquartile ranges; 25-75th percentile). Muscle strength, muscle strength endurance and motor performance are only presented for the dominant leg.
CMP: chronic musculoskeletal pain; GJH: generalized joint hypermobility; PT/BW: peak torque/body weight; TW: total work.
[a, b]Values with the same superscripts represent homogenous subsets.

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TABLE III.—*Hierarchical regression analysis with muscle strength, muscle strength endurance, motor performance and physical activity level as dependent variables.*

Variables	Muscle strength						Motor performance		
	Extension			Flexion					
	B	P	CI	B	P	CI	B	P	CI
Step 1									
CMP (yes/no)	-24.47	0.07	-51.26 to 2.32	-22.88	0.01*	-40.36 to -5.40	-40.50	<0.01*	-55.18 to -25.83
GJH (yes/no)	14.50	0.36	-16.69 to 45.69	-0.49	0.96	-20.83 to 19.86	-1.98	0.82	-19.06 to 15.10
Age	7.58	0.01*	1.62 to 13.55	2.28	0.25	-1.61 to 6.17	-0.21	0.90	-3.48 to 3.06
Gender	-4.58	0.77	-35.19 to 26.03	-6.12	0.54	-26.09 to 13.84	-18.30	0.03*	-35.07 to -1.54
Step 2									
PHODA-youth	-0.24	0.01*	-0.41 to -0.08	-0.17	<0.01*	-0.27 to -0.06	-0.17	<0.01*	-0.26 to -0.08
Step 3									
CMP×GJH	-63.24	0.04*	-123.52 to -2.96	-37.02	0.07*	-76.35 to 2.30	2.26	0.89	-30.55 to 35.07
Separate analysis CMP=1 (CMP)									
GJH (yes/no)	-19.60	0.48	-76.34 to 37.14	-20.74	0.19	-52.31 to 10.83			
Age	2.76	0.71	-12.66 to 18.18	0.68	0.87	-7.90 to 9.26			
Gender	-49.94	0.21	-129.88 to 30.00	-20.59	0.35	-65.07 to 23.89			
PHODA-youth	-0.25	0.02*	-0.46 to -0.04	-0.15	0.01*	-0.27 to -0.04			
Separate analysis CMP=0 (no CMP)									
GJH (yes/no)	40.90	0.03*	4.61 to 77.18	16.09	0.21	-9.51 to 41.69			
Age	6.25	0.06	-0.16 to 12.67	0.82	0.72	-3.70 to 5.35			
Gender	-7.02	0.67	-34.39 to 28.09	-12.26	0.29	-35.13 to 10.62			
PHODA-youth	-0.16	0.48	-0.60 to 0.28	-0.18	0.26	-0.49 to 0.13			
	Muscle strength endurance						Physical Activity level		
	Extension			Flexion					
	B	P	CI	B	P	CI	B	P	CI
Step 1									
CMP (yes/no)	-0.20	0.02*	-0.36 to -0.04	-0.20	<0.01*	-0.34 to -0.06	7.8×10^3	0.53	-16.7×10^3 to 32.2×10^3
GJH (yes/no)	0.03	0.74	-0.15 to 0.22	0.009	0.91	-0.16 to 0.17	3.8×10^3	0.79	-24.2×10^3 to 31.7×10^3
Age	0.04	0.04*	0.002 to 0.07	0.03	0.05*	0.00 to 0.07	-4.5×10^3	0.10	-9.8×10^3 to 0.9×10^3
Gender	-0.07	0.47	-0.25 to 0.11	-0.06	0.44	-0.22 to 0.10	-32.9×10^3	0.02*	-60.7×10^3 to -5.1×10^3
Step 2									
PHODA-youth	-0.002	<0.01*	-0.003 to -0.001	-0.001	<0.01*	-0.002 to -0.001	-0.1×10^3	0.07	-0.3×10^3 to 0.01×10^3
Step 3									
CMP×GJH	-0.28	0.12	-0.63 to 0.07	-0.15	0.35	-0.47 to 0.17	-35.5×10^3	0.21	-90.7×10^3 to 19.8×10^3

Muscle strength, muscle strength endurance, and motor performance are only presented for the dominant leg. Muscle strength endurance extension and flexion were log transformed prior to the analyses. Values presented are the regression coefficient (B) and 95% confidence interval's (CI). P values from the separate variables are from the *t*-tests in the equation.
CMP: chronic musculoskeletal pain, GJH: generalized joint hypermobility, PHODA-youth: Photographs Series of Daily Activities for youth.
*Statistically significant.

Motor performance

The results in the first step for motor performance showed that after adding having CMP, GJH, age, and gender only having CMP was associated with decreased motor performance (B=-40.50; P<0.01) and male adolescents had a significant higher score on the SLHD (B=18.30 P=0.03). In the second step, perceived harmfulness was associated with motor performance, indicating that higher scores of perceived harmfulness were associated with decreased motor performance (B=-0.17, P<0.01). In the third step, the interaction term CMP*GJH was added, but no significant association was found (Table III).

Physical activity level

For PAL the first step showed that female adolescents had decreased levels of PAL (B=-32.9×10^3; P=0.02). No significant association was found for having CMP. After adding perceived harmfulness in the second step and the interaction term CMP*GJH in the third step, no significant associations were found (Table III).

Discussion

This study showed that adolescents with CMP had decreased muscle strength, decreased muscle strength en-

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durance, and lower motor performance compared to adolescents without CMP. In contrast to our expectations, the results indicated that adolescents with G-HSD/hEDS do not have lower physical functioning levels compared to non-hypermobile adolescents with CMP. Furthermore, this study could not confirm lower objectively PAL in adolescents with CMP (with/without GJH) compared to adolescents without CMP (with/without GJH). In addition, higher levels of pain-related fear, which was found in adolescents with CMP, were associated with decreased muscle strength, muscle strength endurance, and motor performance. However, in contrast to our expectations no difference between the influence of pain-related fear on physical functioning in adolescents with G-HSD/hEDS compared to non-hypermobile adolescents with CMP was found.

The findings of the current study were consistent with results of previous studies who found decreased abdominal and back muscle strength endurance and a reduction in motor performance, using the drop vertical jump test, in adolescents with CMP compared to pain-free controls.[4, 35, 36] Furthermore, other studies also showed decreased knee flexor and extensor muscle strength and reduced motor performance in children and adolescents with G-HSD/hEDS compared to healthy controls.[12, 14] In addition, the current study used the SLHD as dynamic performance test determined by coordination, balance, and joint stability,[28] whereas Schubert-Hjalmarsson *et al.*[14] measured motor performance with another performance test (Bruininks-Oseretsky test of motor proficiency). However, the results of the current study did not support the hypothesized negative impact of having GJH and CMP on physical functioning compared to CMP alone. A possible explanation for these findings could be that the selected CMP population in this study was included in an university outpatient rehabilitation clinic specialized in pain rehabilitation and already experiencing long-term disabling pain complaints resulted in a decline of daily functioning and deconditioning in both the hypermobile and non-hypermobile adolescents with CMP. This deconditioning may have resulted in decreased muscle strength, decreased muscle strength endurance, and lower motor performance in hypermobile and non-hypermobile adolescents with CMP compared to adolescents without CMP, but no differences occurred between the hypermobile and non-hypermobile adolescents with CMP. These results are based on only a small number of adolescents with G-HSD/hEDS (N.=9) and should therefore be treated with caution. The results also showed that muscle strength of the knee extensors was increased in adolescents with GJH and without CMP compared to non-hypermobile adolescents without CMP, which was also found in a female population (aged 27.2-28.1 years) without CMP and with/without GJH.[37] It is hypothesized that this increased muscle strength is beneficial for joint stability to compensate for joint laxity and might act as a protecting mechanism in preventing the occurrence of musculoskeletal pain. An unexpected finding was that there were no differences in objectively measured PAL between the different subgroups. This was in contrast with other studies showing lower levels of objectively assessed and subjectively reported PAL in adolescents with CMP or G-HSD/hEDS compared to healthy adolescents.[14, 38, 39] However, another study also found a similar subjective PAL in adolescents with and without CMP.[40] In addition, the studies of Stommen *et al.*[40] and Schubert-Hjalmarsson *et al.*[14] showed that pain-free adolescents appeared to be more active in sports or outdoor games. This last finding could also be of interest in the current population, though due to the absence of continuous physical activity measurements during contact sports and/or swimming we could not differentiate between the different intensities of PAL. Thus, it appeared that adolescents with CMP and with/without GJH do not differ in PAL compared to adolescents without CMP and with/without GJH, despite the decreased muscle strength and lower motor performance. The findings of the decreased muscle strength and lower motor performance might be influenced by pain experienced during testing and psychological factors, such as pain catastrophizing and pain-related fear. Adolescents with CMP might decide to stop or perform submaximal, resulting in a lower score.[41] Therefore, in future studies it is important to distinguish whether physical deconditioning or submaximal performance due to pain and/or pain-related fear is accounting for the physical outcome.

Furthermore, the results of the current study showed that pain-related fear in adolescents with CMP, independent from having GJH or not, is associated with decreased muscle strength, muscle strength endurance, and motor performance. This supports previous findings of the growing evidence on the negative association of pain-related fear on disability in adolescents with CMP.[42, 43] Furthermore, other studies in subjects with hEDS also showed heightened fear of pain and movement, using the Tampa Scale of Kinesiophobia.[15, 17] In addition, Rombaut *et al.*[44] reported increased fear of falling in adults with hEDS compared to pain-free non-hypermobile controls, which might contribute to further muscle weakness and postural instability. However, as mentioned before, pain-related fear could

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also lead to a submaximal performance on the physical outcome tests resulting in a lower score. In addition, there were no differences in pain-related fear between adolescents with G-HSD/hEDS compared to non-hypermobile adolescents with CMP. This finding supported a previous study who also found no differences in pain-related fear, measured with the Fear of Pain Questionnaire-Child report between hypermobile and non-hypermobile adolescents with CMP.[45]

In this study we used G-HSD/hEDS as an umbrella term to cover the new and old (Joint Hypermobility Syndrome / hypermobility type of Ehlers-Danlos syndrome) nomenclature of GJH-related disorders with CMP. It should be noted that it is currently unknown what the consequences are of these new unified criteria for patient outcomes and disease distinctive.

To our knowledge this was the first study focusing on the individual role of having GJH and having CMP on physical functioning within patients with G-HSD/hEDS and the additional role of pain-related fear. Therefore, this study allowed to differentiate between both the physical components in tandem with pain-related fear in adolescents with G-HSD/hEDS compared to adolescents with CMP. These results suggested that once adolescents have CMP, despite being hypermobile or not, the level of pain-related fear is the contributing factor to diminished physical functioning.

Limitations of the study

The study showed several limitations, which should be addressed. First, the limited number of adolescents with CMP and GJH and adolescents without CMP and GJH. Therefore, the results should be treated with caution. However, the prevalence of GJH in the general population (18%) and GJH in the CMP population (30%) is comparable to other studies performed in the Dutch adolescent population, despite the use of different cut-off points.[45, 46] Further research should be conducted in larger groups to confirm the current findings. Second, the absence of continuous physical activity measurements due to contact sports and/or swimming might result in an underestimation of the adolescent's actual PAL. Especially in the group of adolescents without CMP, who reported more non-wearing time due to different sports than the adolescents with CMP. Third, the relatively large number of analyses performed leads to an increased Type I error. The fourth limitation is the cross-sectional design of the current study, which meant no causal relationships could be confirmed. Future studies should employ longitudinal designs to examine associations over time in adolescents with GJH before the onset of CMP. Differences in physical and psychological functioning in adolescents who will or will not develop CMP might be important determinants for prevention of the development of CMP. Another limitation could be that we did not include other potential confounders to our analysis. A previous study showed that a longer pain duration was associated with lower physical functioning levels in adolescents with chronic pain.[39] Furthermore, several studies showed that Caucasian adolescents have higher levels of physical functioning compared to African-American and Hispanic adolescents.[47, 48] Since, the overall majority of our adolescents are Caucasian (data not shown) we did not add ethnicity as confounder in the regression models. The final limitation is that we need to consider that this study included adolescents with long-term disabling pain complaints, in an university outpatient rehabilitation clinic specialized in pain rehabilitation. Therefore, our results might be specific to this population in this setting and this is important to consider when generalizing the results to other populations or settings.

This study also has clinical implications. Several studies proposed multidisciplinary rehabilitation treatment (MRT) for adolescents with G-HSD/hEDS that reduce disability.[49-51] The studies of Rahman *et al.*[50] and Bathen *et al.*[49] included cognitive-behavioral therapy (CBT), not specifically aimed at reducing pain-related fear, alongside with physical therapy. Improvements were found in muscle strength and muscle strength endurance, a reduction of kinesiophobia, a decrease in levels of anxiety, depression, and catastrophizing thoughts, and an increase in self-efficacy. The findings of this study showed that physical functioning in hypermobile as well as non-hypermobile adolescents with CMP was diminished and that the level of pain-related fear was contributing. These results support previous findings in the literature who showed that psychological distress, such as anxiety and depression, had a strong association with disability in patients with G-HSD/hEDS.[52] Therefore, it seemed to imply that in future MRT for adolescents with G-HSD/hEDS it is important to focus also on psychological components, such as pain-related fear, catastrophizing thoughts, and generalized anxiety. Furthermore, it might be advisable to include other important constructs of functional disability in adolescents with G-HSD/hEDS such as multi-systemic dysfunction and fatigue.[53]

Conclusions

In conclusion, adolescents with CMP had decreased muscle strength and motor performance associated with increased

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levels of pain-related fear compared to adolescents without CMP. Contrary to expectations, no differences were found in physical functioning and pain-related fear between adolescents with G-HSD/hEDS compared to adolescents with CMP. Furthermore, no differences in PAL was observed between adolescents with/without CMP compared to pain-free controls. These results seemed to suggest that future MRT for adolescents with G-HSD/hEDS should also focus on psychological components, such as pain-related fear and generalized anxiety.

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