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Somatic symptoms, pain, catastrophizing and the association with disability among children with heritable connective tissue disorders

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Abstract

The aim of the present study was to investigate the nature and prevalence of nonspecific somatic symptoms, pain and catastrophizing in children with Heritable Connective Tissue Disorders (HCTD), and to determine their association with disability. This observational, multicenter study included 127 children, aged 4–18 years, with Marfan syndrome (MFS) (59%), Loeys-Dietz syndrome (LDS) (8%), Ehlers-Danlos syndromes (EDS) (12%) and hypermobile Ehlers-Danlos syndrome (hEDS) (23%). The assessments included the Children's Somatization Inventory or parent proxy (CSI, PCSI), pain visual-analogue scale (VAS), SUPERKIDZ body diagram, Pain Catastrophizing Scale Child or parent proxy (PCS-C, PCS-P) and Childhood Health Assessment Questionnaire (CHAQ-30). Data from children aged ≥8 years were compared to normative data. In children ≥ 8 years ($n = 90$), pain was present in 59%, with a median of 4 (IQR = 3–9) pain areas. Compared to normative data, the HCTD group reported significantly higher on the CSI ($p \leq 0.001$, d = 0.85), VAS pain intensity ($p \leq 0.001$, d = 1.22) and CHAQ-30 ($p \leq 0.001$, d = 1.16) and lower on the PCS-C ($p = 0.017$, d = −0.82) and PCS-P ($p \leq 0.001$, d = −0.49). The intensity of nonspecific somatic symptoms and pain explained 45% of the variance in disability ($r^2 = 0.45$ F(2,48) = 19.70, $p \leq 0.001$). In children ≤ 7 years ($n = 37$), pain was present in 35% with a median of 5(IQR = 1–13) pain areas. The mean(*SD*) VAS scores for pain intensity was 1.5(2.9). Functional disability was moderately correlated to the number of pain areas ($r = 0.56$, $p \leq 0.001$), intensity of nonspecific somatic symptoms ($r = 0.63$, $p \leq 0.001$) and pain ($r = 0.83$, $p \leq 0.001$). In conclusion, this study

A complete list of the Pediatric Heritable Connective Tissue Study Group members appears in the Acknowledgements.

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supports the need for comprehensive assessment of nonspecific somatic symptoms, pain, and disability in children with HCTD to allow tailored treatment.

KEYWORDS
disability, heritable connective tissue disorders, pain, somatic symptoms

1 | INTRODUCTION

Heritable Connective Tissue Disorders (HCTD) are characterized by pathological connective tissue fragility in various organ systems, such as heart, blood vessels, skin, joints, bone, eyes and lungs (Meester et al., 2017). Typical examples of HCTD are Marfan syndrome (MFS) (Loeys et al., 2010), Loeys-Dietz syndrome (LDS) (Van Laer et al., 2014) and Ehlers-Danlos syndromes (EDS) (Malfait et al., 2017). From previous research it is known that children and their parents perceived substantial impact of HCTD on daily functioning resulting in high rates of perceived disability (Warnink-Kavelaars, Beelen, Dekker, et al., 2019; Warnink-Kavelaars, Beelen, Goedhart, et al., 2019; Wesley et al., 2020). Parents highlighted that daily activities are challenging for children with HCTD of all ages (Wesley et al., 2020). Several factors may contribute to the disability perceived, including somatic symptoms, pain, and coping with pain.

Pain is one of the major complaints in adults with HCTD. Pain complaints are often chronic (lasting ≥3 months) and widespread (Meester et al., 2017; Syx et al., 2017). Children and adolescents with HCTD have been reported to show significantly higher pain levels in comparison to healthy peers (Warnink-Kavelaars et al., 2021). In semi-structured interviews, adolescents with MFS reported that the presence of pain was one of the factors that limited going to school, playing sports and maintaining friendships (Warnink-Kavelaars, Beelen, Goedhart, et al., 2019), a finding that was corroborated by the results of a later survey study among parents of children with MFS, EDS and hypermobile Ehlers-Danlos syndrome (hEDS) (Wesley et al., 2020). Although pain may be an important factor in the development of disability, knowledge on the prevalence, severity, location, and nature of pain and its association to disability in children with HCTD is sparse.

Nonspecific somatic symptoms, such as headache, nausea, palpitations, constipation, diarrhea, dizziness, faintness and others have been regularly reported in adults with hEDS, MFS and LDS (De Wandele et al., 2013; Inayet et al., 2018; Wang et al., 2021). One study performed in children with hEDS showed that the presence of a high number of nonspecific somatic symptoms is the strongest predictor for disability (Tran et al., 2020). So far, except for hEDS, the presence of nonspecific somatic symptoms and its association with disability has not been investigated in children with HCTD.

The perception of pain in adults with MFS and hEDS has been found affected by pain catastrophizing, which means negative thoughts and feelings about pain (Scheper et al., 2015; Speed et al., 2017). Studies in children with chronic pain conditions have shown positive relationships between pain catastrophizing, pain levels and poor functioning (Engel et al., 2013; Pielech et al., 2014). Pain catastrophizing is also identified as a significant predictor of persistent pain and central sensitization in adolescents with chronic pain (Pielech et al., 2014). The prevalence of pain catastrophizing and the relationship of pain catastrophizing with disability in children with HCTD has not yet been investigated.

The current study aimed to investigate the nature and prevalence of nonspecific somatic symptoms, pain and pain catastrophizing in a sample of children with HCTD and among HCTD subgroups. In addition, the association of nonspecific somatic symptoms, pain and pain catastrophizing with disability was studied.

2 | METHODS

2.1 | Study design

This study is a multicenter cross-sectional observational survey study.

2.2 | Participants

Eligible for inclusion were all HCTD children, aged between 4 and 18 years, diagnosed with MFS (Loeys et al., 2010), LDS (Van Laer et al., 2014), genetically confirmed types of EDS (Malfait et al., 2017) and hEDS (Castori et al., 2017). Participants for this study were recruited at the Expert Centers for Marfan syndrome and related Connective Tissue Disorders in the Netherlands, including the University Medical Centers of Amsterdam, Leiden, Groningen, Maastricht and Nijmegen, and the Center for Medical Genetics of the Ghent University Hospital in Belgium. Additionally, participants were recruited through the MFS and EDS patient associations in the Netherlands that announced information on the study on their websites.

2.3 | Measures

2.3.1 | Nonspecific somatic symptoms

The Children's Somatization Inventory (CSI) or the parent version of this questionnaire (P-CSI) was used to evaluate the perceived severity of 35 nonspecific somatic symptoms in children. Participants reported how often they have suffered from each of the listed symptoms in the last 2 weeks. Scores on each item may range from 0 to 4 (0 = not at

all, 4 = a whole lot). The total score is obtained by summing scores on all items and may range from 0 to 140, with higher scores indicating higher intensity of nonspecific somatic symptoms (Meesters et al., 2003). The Dutch version of the CSI has been found a reliable and valid measure for assessing somatization symptoms in children and adolescents (Meesters et al., 2003).

2.3.2 | Pain presence and nature, pain intensity and pain areas

Pain presence was assessed by the question "Do you sometimes have bodily pain related to your disease?" (0 = no, 1 = yes). In addition, if the answer is yes, pain nature by the presence of pain for ≥3 months by the question: "Do you have bodily pain lasting ≥3 months" (0 = no, 1 = yes). Mean pain intensity over the last week was measured by a Visual Analogue Scale (VAS) (Carlsson, 1983) and scored on a 0 to 10 cm scale with 0 cm referring to "no pain" and 10 cm to "very severe pain" (Michaleff et al., 2017). The psychometric properties of a VAS to assess pain have been extensively studied and test–retest reliability and validity have been demonstrated (Sánchez-Rodríguez et al., 2015).

The number of pain areas was assessed by the SUPER-KIDZ body diagram (von Baeyer et al., 2011). Children were asked to indicate the areas on the body diagram where they experienced pain in the past week. A total score was computed by summing the numbers of painful locations (range 0–21) with a higher score indicating a larger amount of pain areas. For analysis, 21 pain areas were grouped into upper extremity, lower extremity, thorax/trunk area and head/neck area. The SUPER-KIDZ has shown good internal consistency and satisfactory test–retest reliability (Luca et al., 2017).

2.3.3 | Pain catastrophizing

The Pain Catastrophizing Scale Child version (PCS-C) and its parent version (PCS-P) were used to assess negative thoughts and feelings about pain in children (Crombez et al., 2003; Goubert et al., 2006). The scale consisted of 13 statements beginning with the phrase "When I have pain…." (PCS-C) or "When my child is in pain…."(PCS-P). All items are scored on a 5-point Likert scale with scores ranging from 0 to 4 (0 = not at all, 4 = extremely) (Sullivan et al., 1995). A total score and scores on three subscales assessing types of catastrophizing can be calculated: Rumination (item 8–10: thoughts and inability to impede pain-related thoughts), Magnification (items 6–7, 13; intensification of unpleasantness of pain and expectancy of negative outcomes), and Helplessness (item 1–5, 12: inability to cope with the pain). For both the PCS-P and PCS-C, items are summed up to create a total score that may range between 0 and 52, with higher scores indicating higher levels of pain catastrophizing (Crombez et al., 2003; Goubert et al., 2006). The PCS-C and PCS-P has been found to show good-to-excellent validity and reliability (Cederberg et al., 2019a; Cederberg et al., 2019b).

2.3.4 | Functional disability

The Dutch version of the Childhood Health Assessment Questionnaire (CHAQ-30) (Wulffraat et al., 2001) was used to assess functional disability in daily life activities and distinguishes between the following eight domains of functioning: dressing, arising, eating, walking, hygiene, reach, grip and activities. Items are scored on a four point scale (0 = no disability, 3 = disabled). Each domain is covered by a minimum of two and maximum of five items. The highest score of an item within a domain determines the domain score. In case assistance or aids are used, the domain score is increased by 1 point to a maximum of 3. The CHAQ disability index (CHAQ-30 DI) is the mean score on the eight domains and may range from 0 to 3 (Wulffraat et al., 2001). The CHAQ-30 has shown high reliability, validity and responsiveness to change over time (Singh et al., 1994).

2.4 | Procedures

Inclusion took place from February 2019 until January 2021. The Medical Ethics Review Committee of the Amsterdam UMC (reference number W18_346) and the Ethical Committee of Ghent University Hospital (EC2019/1958) approved the study's protocol. Children and parents known to the outpatient clinic were invited by letter, while others applied through the websites of the patient associations. Informed consent was obtained by parents if children were <12 years of age or by parents and children when children were ≥12 and <16 years of age, or by the patients if they were ≥16 years of age. Information about sex, age, nationality and HCTD diagnosis was provided by one of the parents.

If children were ≤7years of age, the parent completed all questionnaires (P-CSI, pain presence, VAS pain intensity, SUPERKIDZ body diagram, PCS-P, and CHAQ-30). If children were ≥8years of age, the child completed all questionnaires (CSI, pain presence, VAS pain intensity, SUPERKIDZ body diagram, PCS-C, CHAQ-30). In addition, the parent completed the PCS-P on his/her child. Completion time was 30–40 min for both parent and child.

2.5 | Statistical analysis

In general, all online survey data were exported from the Castor database (Electronic Data Capture, Ciwit BV, Amsterdam, The Netherlands, 2021) to the Statistical Package for Social Science (SPSS) version 26.0 (IBM Corp. Released, 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, 2019).

The percentage of missing values was <10% for all measures, except for PCS-C (13%). Missing data were missing at random and were not related to sex or age. Chained Equations and Predictive Mean Matching was used to impute missing data (Eekhout et al., 2014).

Data were analyzed separately with respect to age: (1) ≥8 years of age (children from 8 up to and including 17 years of age);

(2) ≤7 years of age (children from 4 up to and including 7 years of age).

2.5.1 | Analyses of children with HCTD ≥8 years of age

Sociodemographic characteristics (i.e., sex, age and nationality) of the HCTD group and subgroups were described using descriptive statistics (M, *SD*). Pain presence, number of pain areas and pain distribution (SUPER-KIDZ body diagram), were described using parametric (normally distributed data) or nonparametric (not normally distributed data) descriptive statistics.

The scores of the CSI, VAS-pain intensity, PCS-C, PCS-P and CHAQ-30 DI of the HCTD- group, MFS-, LDS- EDS-, and hEDS-subgroups were calculated. Then, data of the HCTD-group and MFS- and hEDS-subgroups were compared with representative general population samples. The limited sample size of the EDS and LDS subgroups did not allow comparisons with normative data.

More specifically, the CSI data of our sample were compared with a representative Dutch population sample of 479 children (age M = 12.8, *SD* = 1.39 years) (Meesters et al., 2003), the VAS-pain intensity data to a representative Dutch population sample of 80 children (age M = 8.1, *SD* = 3.6 years) (Wulffraat et al., 2001), the PCS-C and PCS-P data to a representative Flemish population sample of 814 children (age M = 12.4 *SD* = 2.04 years) (Crombez et al., 2003) and 205 children (age M = 12.7 *SD* = 1.65 years) (Goubert et al., 2006), respectively, and the CHAQ-30 DI data to a representative Dutch population of 80 children (age M = 8.1 *SD* = 3.6 years) (Wulffraat et al., 2001). The sample characteristics age and sex of the HCTD-group and the MFS- and hEDS-subgroup were compared with the representative samples using Chi-square tests and *t*-tests, respectively.

Subsequent analyses involved three steps. First, sum scores and subscale scores derived from four the questionnaires of the HCTD group and subgroups MFS and hEDS were compared with the appropriate representative samples, using *t*-tests. Age and sex distribution were compared using t-tests and chi-square tests. The age distribution of the HCTD population differ from the distribution of the representative sample for PCS-P and CSI. The sex distribution differ from the representative sample for VAS-pain intensity and CHAQ-30 DI. Regarding subgroups, the age distribution of the subgroups MFS and hEDS differs from the distribution of the representative sample for VAS-pain intensity and CHAQ-30 DI. In addition, for the hEDS subgroup also for PCS-P, PCS-C and CSI. The sex distribution of the subgroup MFS differ from the representative samples for PCS-P, PCS-C and CSI, whereas there were no differences for subgroup hEDS.

In the second analysis step, the analysis of the HCTD- group were repeated for the MFS- and hEDS-subgroups.

In the third analysis step, a sensitivity analysis was performed due to significant differences in sex (VAS pain intensity, CHAQ-30 DI) and age distribution (PCS-P, CSI) of the HCTD sample and the MFS- and hEDS-subgroups (VAS-pain intensity, PCS-P, PCS-C, CSI and CHAQ-30 DI) compared to normative data. For each questionnaire, the same t-tests were performed in a selected HCTD sample (numbers per selected HCTD samples; VAS pain intensity $n = 86$, PCS-P $n = 55$, CSI $n = 70$, CHAQ-30 DI $n = 86$) that was comparable in sex and age to the normative data. With the exception of age and sex, significant group differences remained significant with highly similar effect sizes.

For all group comparisons, effect sizes were calculated according to Cohen, with values of 0.2, 0.5, and 0.8 defined as thresholds for small, moderate, and large effects, respectively (Andy Field, 2012). Sum scores were analyzed first, and if a significant group difference emerged, a subsequent analysis was performed, aimed at further pinpointing the nature of the group difference by analyzing those subscales. For the analysis of sum scores of the questionnaires a *p*-value of ≤0.05 was considered statistically significant, for the subscale scores. To correct for multiple testing, the analysis of the subscale scores used a *p*-value of ≤0.001 to determine statistical significance.

To explore the association between nonspecific somatic symptoms, pain intensity and pain catastrophizing coping on the one hand, and disability on the other, a multivariable linear regression (backward elimination; probability of F for entry = 0.05 and for removal = 0.10) was performed. The dependent variable was functional disability (CHAQ-30 DI), independent variables were the CSI-total scores, PCS-P and PCS-C total scores and VAS pain intensity scores.

2.5.2 | Analyses of children with HCTD ≤7 years of age

Because of the lack of normative data for this age group and the limited number of participants in the HCTD subgroups, descriptive statistics (M, *SD*) were provided for the scores on the P-CSI, PCS-P and CHAQ-30 DI. The quantity and distribution of pain areas were described with numbers and percentages. To explore the association of nonspecific somatic symptoms, pain intensity, pain areas, pain catastrophizing with disability, Spearman's Rho was used (Andy Field, 2012).

3 | RESULTS

3.1 | Participants

A total of 127 children and their parents agreed to participate in the study. Table 1 shows the sex and age distribution of the HCTD group and the MFS-, LDS-, EDS- and hEDS subgroups. The EDS subgroup comprises children with classical EDS $n = 11$, classical-like EDS $n = 1$, vascular EDS $n = 1$, dermatosparaxis EDS $n = 1$ and arthrochalasia EDS $n = 1$) and 29 (23%) with hEDS. A total of 37 children (29%) were between 4 and 7 years of age and 90 children (71%) were ≥8 years of age (Table 1).

TABLE 1 Participant characteristics.

	HCTD	MFS	LDS	EDS	hEDS
Number of children, *n* (%)					
All ages	127(100)	75(59)	8(6)	15(12)	29(23)
≤7 years	37(29)	23(62)	2(5)	3(8)	9(24)
≥8 years	90(71)	52(57)	6(7)	12(13)	20(22)
Mean age (*SD*)					
All ages	10.5(3.8)	10.4(4.1)	10.4(4.1)	10.5(4.1)	10.5(4.1)
≤7 years	5.7(1.2)	5.6(1.2)	5.6(1.2)	5.3(1.2)	5.3(1.2)
≥8 years	12.8(2.8)	12.5(2.9)	12.5(2.9)	13.6(2.8)	11.0(2.8)
Number of females, *n* (%)					
All ages	52(41)	23(31)	5(62)	7(47)	27(93)
≤7 years	15(40)	7(30)	1(50)	2(67)	5(56)
≥8 years	37(41)	16(31)	4(67)	5(42)	12(60)

Abbreviations: EDS, Ehlers-Danlos Syndromes; HCTD, heritable connective tissue disorders; hEDS, hypermobile Ehlers-Danlos syndrome; LDS, Loeys Dietz syndrome; MFS, Marfan syndrome; *n*, number; %, percentage; *SD*, standard deviation.

3.2 | Children with HCTD ≥8 years of age

3.2.1 | Nonspecific somatic symptoms (CSI)

Tables 2 and 3 show somatic symptoms in children with HCTD assessed with the CSI of the HCTD group, subgroups and normative data of a representative sample. Children with HCTD reported significantly higher CSI scores compared to the normative data indicating higher intensity of nonspecific somatic symptoms. Both children with MFS and hEDS showed significantly higher CSI scores than the normative data children with hEDS scored significantly higher than children with MFS.

3.2.2 | Pain presence and nature, pain intensity (VAS) and pain areas (SUPERKIDZ body diagram)

Table 4 and Figure 1 show pain presence, pain intensity and pain areas in the HCTD group, subgroups and normative data of a representative sample.

Pain complaints were present in 53 (59%) out of 90 HCTD children and 35 (39%) of them reported pain complaints lasting ≥3 months. HCTD children reported significantly higher VAS scores for pain intensity during the past week compared to the normative data. Both the MFS and hEDS subgroup reported significantly higher VAS pain scores compared with the normative and VAS pain scores of children with hEDS were significantly higher than those reported by children in the MFS subgroup.

The body pain areas in the 53 children who reported pain were widespread and distributed across the body.

3.2.3 | Pain catastrophizing reported by the child (PCS-C)

Tables 2 and 3 show *PCS-C* scores of the *HCTD* group, subgroups and normative data of a representative sample.

Compared to the normative sample, PCS-C total scores and subset scores were significantly lower in children with HCTD, indicating that children with HCTD have less negative thoughts and feelings about pain than those in the normative sample (Tables 2 and 3). Comparison of the MFS and hEDS subgroups with normative data showed that the MFS subgroup had significantly lower Total scores and lower scores on all PCS-C subsets, whereas the hEDS subgroup did not significantly differ from the normative sample on any of the scores derived from the PCS-C (Table 3). The hEDS subgroup had significantly higher Total score and Helplessness subset scores compared to those obtained in the MFS subgroup.

3.2.4 | Pain catastrophizing reported by the parent (PCS-P)

Tables 2 and 3 show PCS-P scores of the HCTD group, subgroups and normative data of *a* representative sample.

The PCS-P scores were significantly lower compared to normative data for the total score and subsets Rumination, Magnification and Helplessness, indicating fewer negative thoughts and feelings about pain in their children compared to normative data. Comparison of the MFS parent subgroup with normative data showed significant lower catastrophizing scores on all PCS-P subsets. The hEDS parent subgroup scored significant lower on subset Magnifications while other subsets (Rumination, Helplessness) were not significantly different compared to normative data. Analysis among the subgroup MFS and hEDS showed no significant differences on total scores and subset scores.

3.2.5 | Pain catastrophizing reported by child versus parent

No significant differences in pain catastrophizing were found between reports by the child (PCS-C) or the parent (PCS-P), neither on total scores nor in subset scores (Rumination, Magnification, Helplessness).

TABLE 2 Somatic symptoms, pain, catastrophizing and functional disability in children with HCTD ≥8 years of age.

	HCTD = 90	MFS = 52	hEDS = 20	EDS = 12	LDS *n* = 6
Somatic symptoms (CSI)					
Age in years, mean(*SD*)	12.5(2.8)	12.5(2.9)	11(2.8)	13.6(4.2)	11.0(3.4)
Sex, *n*(%) female	36(40)	16(31)	12(60)	5(42)	4(67)
Total score	24.9(22.1)	17.6(15.6)	47.3(25.8)	22.0(16.1)	19.5(9.9)
Pain intensity (VAS)					
Age in years	12.5(2.8)	12.5(2.9)	11(2.8)	13.6(4.2)	12.5(2.7)
Sex, *n*(%) female	36(40)	16(31)	12(60)	5(42)	4(67)
Score past 7 days	2.6(3.0)	1.4(2.4)	4.8(3.3)	3.5(2.8)	3.3(2.6)
Pain catastrophizing (PCS-C)					
Age in years	12.5(2.8)	12.5(2.9)	11(2.8)	13.6(4.2)	12.5(2.7)
Sex, *n*(%) female	36(40)	16(31)	12(60)	5(42)	4(67)
Total score	12.9(7.7)	11.2(6.8)	16.9(6.8)	12.4(8.1)	16.3(5.1)
Rumination	6.2(3.8)	5.8(3.8)	7.4(2.9)	5.4(3.8)	8.2(3.7)
Magnification	2.0(1.8)	1.6(1.5)	2.4(2.4)	2.3(1.7)	2.8(1.4)
Helplessness	4.7(3.4)	3.8(2.8)	7.1(3.3)	4.8(4.2)	5.3(1.7)
Pain catastrophizing (PCS-P)					
Age in years	12.5(2.8)	12.5(2.9)	11(2.8)	13.6(4.2)	11.0(3.4)
Sex, *n*(%) female	36(40)	16(31)	12(60)	5(42)	4(67)
Total score	11.1(8.7)	10.8(7.0)	12.9(11.0)	12.3(9.4)	14.2(13.6)
Rumination	5.9(4.0)	5.6(3.6)	6.7(4.5)	5.7(4.1)	6.2(5.8)
Magnification	2.0(1.9)	2.1(1.8)	1.6(2.1)	2.3(1.9)	2.5(1.4)
Helplessness	3.8(4.0)	3.0(3.0)	4.7(5.0)	4.4(4.4)	5.5(6.9)
Functional ability (CHAQ-30)					
Age in years mean(*SD*)	12.5(2.8)	12.5(2.9)	11(2.8)	13.6(4.2)	12.5(2.7)
Sex, *n*(%) female	36(40)	16(31)	12(60)	5(42)	4(67)
Disability index	0.91(0.77)	0.72(0.76)	1.56(0.52)	0.80(0.72)	0.63(0.49)

Abbreviations: CHAQ-30, Childhood Health Assessment Questionnaire; CSI, children's somatization inventory; EDS, Ehlers-Danlos Syndromes; HCTD, heritable connective tissue disorders; hEDS, hypermobile Ehlers-Danlos syndrome; LDS, Loeys Dietz syndrome; MFS, Marfan syndrome; *n*, number; PCS-C, pain catastrophizing scale—children; PCS-P, pain catastrophizing scale—parents; *SD*, standard deviation.

3.2.6 | Functional disability (CHAQ-30)

Tables 2 and 3 show CHAQ-30 DI scores of the HCTD group, subgroups and normative data of a representative sample.

The CHAQ-30 DI was significantly higher in children with HCTD, indicating higher level of disability, compared to Dutch normative data (Tables 2 and 3). Both subgroups MFS and hEDS scored significantly higher compared to normative data. Analysis among the subgroup MFS and hEDS showed that children with hEDS had significant higher CHAQ-30 DI than subgroup MFS.

3.2.7 | Multivariate regression analysis on functional disability

Table 5 shows the multivariate regression analysis. Multivariate regression analysis showed that 45% of the variance in functional disability was explained by the intensity of nonspecific somatic symptoms (CSI Total score) and pain intensity (VAS) ($R^2 = 0.45$ F(2,48) = 19.70, $p \leq 0.001$). Pain catastrophizing did not significantly contribute to functional disability (Table 5).

3.3 | Children with HCTD ≤7 years of age

Table 6 shows the symptomatic symptoms, pain, catastrophizing, and functional disability in children ≤7 years of age. Pain was present in 13 out of 37 (35%) children, and 11 out of 37 (30%) reported pain lasting ≥3 months (Table 4). The mean VAS scores for pain intensity during the past week was 1.5 (*SD* 2.9., range 0–9.0) (Table 6).The median number of pain areas was 5 (IQR 1–13) and were distributed across the upper extremity (32%), the lower extremity (29%) and the thorax/trunk area (23%) (Figure 1).

Functional disability in HCTD children of 4–7 years was moderately to strongly correlated to the number of pain areas reported in the SUPERKIDZ Body diagram ($r = 0.56$, $p \leq 0.001$), perceived intensity of nonspecific somatic symptoms on the P-CSI ($r = 0.63$, $p \leq 0.001$) and the intensity of pain (VAS) ($r = 0.83$, $p \leq 0.001$).

TABLE 3 Analysis of somatic symptoms, pain, catastrophizing, and functional disability in HCTD children to normative data and among HCTD subgroups.

					HCTD vs. normative data		MFS vs. normative data		hEDS vs. normative data		MFS vs. hEDS data	
	HCTD	MFS	hEDS	Normative data	*p*-value	Effect size Cohens' *d*	*p*-value	Effect size Cohens' *d*	*p*-value	Effect size Cohens' *d*	*p*-value	Effect size Cohens' *d*
Somatic symptoms (CSI)												
n	90	52	20	479								
Total score	24.9(22.1)	17.6(15.6)	47.3(25.8)	10.2(10.4)	<0.001	0.85	0.003	0.56	<0.001	3.33	<0.001	0.78
Pain intensity (VAS)												
n	90	52	20	80								
Score past 7 days	2.6(3.0)	1.4(2.4)	4.8(3.3)	0.0(0.2)	<0.001	1.22	<0.001	0.82	<0.001	2.05	<0.001	1.37
Pain catastrophizing (PCS-C)												
n	90	52	20	814								
Total score	12.9(7.7)	11.2(6.8)	16.9(6.8)	16.8(8.8)	0.017	−0.82	<0.001	-0.71	0.964	0.01	<0.001	0.90
Rumination	6.2(3.8)	5.8(3.8)	7.4(2.9)	7.2(3.6)	0.177	−0.33	0.015	−0.38	0.829	0.06	0.094	0.47
Magnification	2.0(1.8)	1.6(1.5)	2.4(2.4)	3.6(2.6)	0.001	−0.67	<0.001	−0.94	0.03	0.40	0.177	0.47
Helplessness	4.7(3.4)	3.8(2.8)	7.1(3.3)	6.1(4.1)	0.062	−0.58	<0.001	−0.66	0.24	0.27	<0.001	1.08
Pain catastrophizing (PCS-P)												
n	90	52	20	205								
Total score	11.1(8.7)	10.8(7.0)	12.9(11.0)	15.7(9.9)	<0.001	−0.49	<0.001	−0.57	0.245	−0.27	0.435	−0.23
Rumination	5.9(4.0)	5.6(3.6)	6.7(4.5)	7.8(4.2)	<0.001	−0.65	<0.001	−0.56	0.281	−0.25	0.283	−0.27
Magnification	2.0(1.9)	2.1(1.8)	1.6(2.1)	2.9(2.4)	<0.001	−0.53	0.022	−0.38	0.020	−0.58	0.317	0.26
Helplessness	3.8(4.0)	3.0(3.0)	4.7(5.0)	5.0(4.3)	0.022	−0.29	<0.001	−0.54	0.77	−0.06	0.167	−0.41
Functional ability (CHAQ-30)												
n	90	52	20	80								
Disability index	0.91(.77)	0.72(0.76)	1.56(0.52)	0.20(0.4)	<0.001	1.16	<0.001	0.86	<0.001	2.39	<0.001	2.93

Note: Cohens' *d* = effect sizes with values 0.2, 0.5, and 0.8 defined as the thresholds for small, moderate and large effects. A *p*-value of ≤ 0.05 was considered statistically significant.
Abbreviations: CHAQ 30, Childhood Health Assessment Questionnaire; CSI, children's somatization inventory; EDS, Ehlers-Danlos syndromes; HCTD, hereditary connective tissue disorders; hEDS, hypermobile Ehlers-Danlos syndrome; LDS, Loeys Dietz syndrome; MFS, Marfan syndrome; *n*, number; PCS-C, pain catastrophizing scale-children; PCS-P, pain catastrophizing scale-parents; *SD*, standard deviation.

TABLE 4 Pain in children with HCTD assessed by questionnaires and the SUPERKIDZ body diagram.

	HCTD	MFS	hEDS	EDS	LDS
Children with pain, *n* (%)					
All ages	66(52)	27(36)	21(72)	13(87)	5(63)
≤7 years	13(35)	5(22)	6(67)	6(67)	0(0)
≥8 years	53(59)	22(42)	15(75)	11(92)	5(63)
Children with pain ≥3 months, *n* (%)					
All ages	46(36)	16(21)	19(66)	9(60)	2(25)
≤7 years	11(30)	3(13)	6(67)	2(67)	0(0)
≥8 years	35(39)	13(25)	13(65)	7(58)	2(33)
Number of pain areas, body chart median(IQR)					
All ages	5(3–10)	3(1.8–5)	10(5.5–13.5)	5(2–8)	7(2–12.5)
≤7 years	5(1–13)	0(0–4.5)	13(10.5–14.5)	2(1-n.a.)	n.a.
≥8 years	4(3–9)	3(2–5)	8(5–11)	3(3–6)	7(2–9)

Note: ≤7 years = children from 4 up to and including 7 years of age, ≥ 8 years = children from 8 up to and including 17 years of age.
Abbreviations: EDS, Ehlers-Danlos syndromes; HCTD, hereditary connective tissue disorders; hEDS, hypermobile Ehlers-Danlos syndrome; IQR, interquartile range; LDS, Loeys Dietz syndrome; MFS, Marfan syndrome; *n*, number; n.a., not applicable; %, percentage.

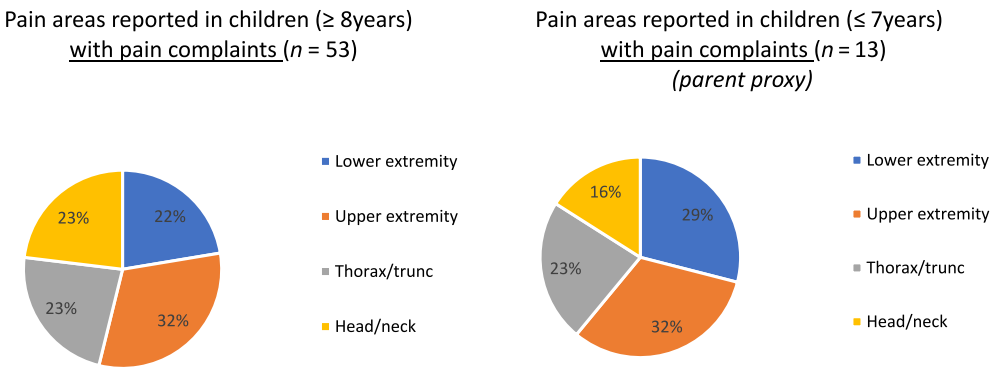

FIGURE 1 Pain areas indicated in children with pain by using the SUPER-KIDZ body diagram.

TABLE 5 Multivariable-adjusted association for somatic symptoms, pain intensity and catastrophizing to disability.

Effects	Estimate	*SE*	Standardized β	95%CI for β		*p*-value
Model 1 ($r^2 = 0.47$)						
Intercept	0.393	0.136		0.126.	0.660	0.004
Somatic symptoms (CSI)	0.007	0.003	0.330	0.001	0.012	0.015
Pain catastrophizing parent (PCS-P)[a]	−0.001	0.006	−0.022	−0.013	0.011	0.853
Pain catastrophizing Child (PCS-C)[a]	−0.007	0.007	−0.125	−0.022	0.007	0.312
Pain intensity (VAS)	0.091	0.023	0.499	0.046	0.136	<0.001
Model 2 ($r^2 = 0.45$)						
Intercept	0.298	0.105		0.092	0.505	0.005
Somatic symptoms (CSI)	0.006	0.003	0.282	0.001	0.011	0.023
Pain intensity (VAS)	0.090	0.022	0.496	0.047	0.134	<0.001

Note: Dependent variable; CHAQ-30 DI (SQRT transformation due to normality assumption). A *p*-value of ≤0.05 was considered statistically significant. r^2 represents the proportion of the variance for a dependent variable that's explained by an independent variable.
Abbreviations: CSI, children's somatization inventory; PCS-C, pain catastrophizing scale—children; PCS-P, pain catastrophizing scale—parents.
[a]Removed; probability of F criteria ≥ 0.100.

4 | DISCUSSION

We investigated nonspecific somatic symptoms, pain, catastrophizing and the associations with disability in children with HCTD. In children ≥8 years of age, we demonstrated that: (1) children reported significantly higher intensity of nonspecific somatic symptoms, pain and disability compared to normative data with large effect sizes; (2) in line with the findings for the total HCTD group, the subgroups of children

TABLE 6 Somatic symptoms, pain, catastrophizing and functional disability in children with HCTD ≤7 years of age.

	HCTD $n = 37$	MFS $n = 23$	LDS $n = 2$	EDS $n = 3$	hEDS $n = 9$
Somatic symptoms (P-CSI)					
Total score	13.8(15.1)	6.3(5.7)	5.0(4.1)	10.6(8.0)	35.7(13.4)
Pain intensity (VAS)					
Score past 7 days	1.5(2.9)	0.4(1.2)	0(0.0)	1.8(1.6)	4.9(3.9)
Pain catastrophizing (PCS-P)					
Total score	9.4(8.5)	7.5(6.5)	8.5(12.0)	9.3(6.6)	14.6(11.7)
Rumination	5.0(4.1)	4.3(3.9)	4.5(6.4)	4.3(2.5)	7.1(4.8)
Magnification	1.4(1.9)	1.2(1.7)	1.5(2.1)	1.3(1.5)	2.0(2.5)
Helplessness	3.0(3.5)	2.1 (2.2)	2.5(3.5)	3.6(3.6)	5.4(5.2)
Functional ability (CHAQ-30)					
Disability index	0.85(0.72)	0.64(0.52)	0.31(0.44)	46(0.79)	1.63(0.70)

Note: All scores are displayed in mean(*SD*).
Abbreviations: CHAQ-30, Childhood Health Assessment Questionnaire; EDS, Ehlers-Danlos syndromes; HCTD, hereditary connective tissue disorders; hEDS, hypermobile Ehlers-Danlos syndrome; LDS, Loeys Dietz syndrome; MFS, Marfan syndrome, *n*, number; *SD*, standard deviation; P-CSI, children's somatization inventory parent proxy; PCS-P, pain catastrophizing scale—parents.

with MFS and hEDS scored significantly higher on nonspecific somatic symptoms, pain and disability compared to normative data with moderate to large effect sizes; (3) comparison among subgroups of children with MFS and hEDS showed that the most adverse sequels regarding pain and functional disability were reported in children with hEDS; (4) the intensity of nonspecific somatic symptoms and pain complaints contributed significantly to disability. Children with HCTD reported a considerable impact of HCTD on daily functioning resulting in higher rates of perceived functional disability compared to healthy peers. The intensity of nonspecific somatic symptoms and pain explained 45% of the variance in functional disability and are therefore important contributing factors.

HCTD children reported a higher intensity of nonspecific somatic complaints. Nonspecific somatic complaints such as headache, stomach pain, dysautonomia and postural orthostatic tachycardia syndrome (POTS) have previously been reported in adults with EDS and hypermobility spectrum disorders (HSD) (a group of conditions related to symptomatic joint hypermobility) (De Wandele et al., 2013) and, based on our findings, appears to be an important complaint in children with HCTD.

More than 50% of the children with HCTD reported to have pain, of which a large number indicated to have pain lasting longer than 3 months. In adults with MFS and EDS, pain is reported to be present in up to 90% of the patients (Nelson et al., 2015; Peters et al., 2001; Velvin et al., 2016; Voermans et al., 2010), suggesting that pain prevalence increases with age.

Children with HCTD indicated to have pain in widespread areas of the body, both in limbs, abdomen and head region. The International Association for the Study of Pain (ISAP) distinguishes three divisions of pain, including nociceptive pain, neuropathic pain and nociplastic pain (Raja et al., 2020). Wide spread pain combined with the chronic character and the presence of nonspecific somatic complaints strongly tends to nociplastic pain which is characterized by an increase sensitivity to normally innocuous stimulus and/or exaggerated response to noxious stimuli (hyperalgesia) (Kosek et al., 2016). No pathophysiological pain model for children with HCTD has been identified yet and the mechanism underling pain is still unknown. It is previously stated that in adults with hEDS pain symptoms may be of "mixed nature" including nociceptive pain, neuropathic pain and nociplastic pain (Syx et al., 2017). Nociceptive pain directly related to affected ligaments and tendons, joints, muscles and connective tissue is frequently encountered and often present in early stages of acute and localized pain. Joint instability due to connective tissue laxity can cause joint dislocations and repetitive soft tissue traumata. (Micro) traumata in joints and maladaptation's in movement have been suggested to explain pain in children and adults with HSD and hEDS (Syx et al., 2017). There are studies supporting neuropathic components in EDS related pain in terms of compression and axonal neuropathies (Syx et al., 2017). In addition to nociceptive and neuropathic components, central sensitization (hyperalgesia) may contribute to the chronic character of generalized pain in individuals with HSD and hEDS (Rombaut et al., 2015; Scheper et al., 2017). Knowledge about pain and its nature can be important for developing tailored made interventions since there are indications that exercises can cause hypoalgesia in adults with various chronic conditions (Da Silva Santos & Galdino, 2018; Rice et al., 2019).

In contrast to the relatively high intensity of nonspecific somatic symptoms and pain complaints, HCTD children reported no pain catastrophizing. Indeed children with HCTD reported significantly less catastrophizing compared to normative samples. These findings are unexpected because studies in children with chronic pain conditions have shown an association between pain catastrophizing, higher pain intensity and poor functioning (Engel et al., 2013; Pielech et al., 2014).

Most differences revealed between HCTD children and normative samples translated into very large-sized effects, suggesting clinical relevant findings. As the complaints are frequent and important

contributing factors to disability, we suggest to systematically monitor nonspecific somatic symptoms and pain complaints in children with HCTD by using standardized questionnaires. Identifying the presence and intensity of these symptoms should be a starting point for setting up tailor-made multidisciplinary treatment programs for children with HCTD. In this study we focused on nonspecific somatic complaints, pain and catastrophizing, which account for 45% of the variance in disability, suggesting that there are other physical, personal and contextual factors that contribute to disability in children as well. Both validated questionnaires and physical measurements could be used to map the clinical profile of children with HCTD and form the basis of tailormade (interdisciplinary) interventions.

Our results should be viewed within the limitations of the study. First, there were no normative data available for children ≤7 years of age, which limited our analysis to descriptive statistics and precluded testing the significance of our findings. Second, the genetically confirmed EDS and LDS subgroups were too small for comparisons with normative data and among subgroups. However, the total sample group of children with HCTD in this study was large and representative. Moreover, this study is the first to investigate nonspecific somatic symptoms, pain, pain catastrophizing, and the associations with disability in children with HCTD. Third, we used parent reports on the diagnostic status of the child. Because most children were recruited by their own physician in one of the expert centers in the Netherlands and Belgium, we are confident that this approach is valid. Nevertheless, in 2017 the international clinical criteria for hEDS were revised (Malfait et al., 2017) and, although our data were collected after 2017, there may be children with hEDS who were not re-diagnosed because they are not regularly treated in one of the expert centers."

5 | CONCLUSION

To conclude, nonspecific somatic symptoms, pain and functional disability are common complaints in children with HCTD. Based on this knowledge, systematic evaluation and follow-up by means of a comprehensive inventory of complaints and subsequent tailor-made interventions in children with HCTD is advised.

AUTHOR CONTRIBUTIONS

Lisanne E. de Koning, Jessica Warnink-Kavelaars, Raoul H. H. Engelbert, Lies Rombaut and Jaap Oosterlaan contributed to the study conception and design. Data collection and analyses were performed by Lisanne de Koning and Jessica Warnink-Kavelaars. The first draft of the article was written by Lisanne de Koning and all authors commented on previous versions of the article. All authors read and approved the final article.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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