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Heritable connective tissue disorders in childhood: Decreased health-related quality of life and mental health

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Abstract

The psychosocial consequences of growing up with Heritable Connective Tissue Disorders (HCTD) are largely unknown. We aimed to assess Health-Related Quality of Life (HRQoL) and mental health of children and adolescents with HCTD. This observational multicenter study included 126 children, aged 4–18 years, with Marfan syndrome (MFS, $n = 74$), Loeys–Dietz syndrome ($n = 8$), molecular confirmed Ehlers–Danlos syndromes ($n = 15$), and hypermobile Ehlers–Danlos syndrome (hEDS, $n = 29$). HRQoL and mental health were assessed through the parent and child-reported Child Health Questionnaires (CHQ-PF50 and CHQ-CF45, respectively) and the parent-reported Strengths and Difficulties Questionnaire. Compared with a representative general population sample, parent-reported HRQoL of the HCTD-group showed significantly decreased Physical sum scores ($p < 0.001$, $d = 0.9$) and Psychosocial sum scores ($p = 0.024$, $d = 0.2$), indicating decreased HRQoL. Similar findings were obtained for child-reported HRQoL. The parent-reported mental health of the

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

HCTD-group showed significantly increased Total difficulties sum scores ($p = 0.01$, $d = 0.3$), indicating decreased mental health. While the male and female MFS- and hEDS-subgroups both reported decreased HRQoL, only the hEDS-subgroup reported decreased mental health. In conclusion, children and adolescents with HCTD report decreased HRQoL and mental health, with most adverse outcomes reported in children with hEDS and least in those with MFS. These findings call for systematic monitoring and tailored interventions.

KEYWORDS
Marfan syndrome, Ehlers–Danlos syndromes, Loeys–Dietz syndrome, childhood, Health-Related Quality of Life, heritable connective tissue disorder

1 | INTRODUCTION

Heritable Connective Tissue Disorders (HCTD) are characterized by pathological connective tissue fragility and multisystemic involvement (Judge & Dietz, 2005; Loeys et al., 2010; Malfait et al., 2017; Meester et al., 2017; Van Laer et al., 2014). The phenotypes of the most common HCTD Marfan syndrome (MFS; Judge & Dietz, 2005; Loeys et al., 2010), Loeys–Dietz syndrome (LDS; Van Laer et al., 2014) and Ehlers–Danlos syndromes (EDS; Malfait et al., 2017) are based on clinical criteria and molecular confirmation. Hypermobile EDS (hEDS) is an exception because the genetic cause has not yet been determined (Malfait et al., 2017). HCTD show similarities in cardiovascular, musculoskeletal, and cutaneous features that can evolve in childhood (Meester et al., 2017). In addition, children and adolescents with HCTD report increased pain and fatigue, decreased general health, and limited activities and participation, compared with their healthy counterparts (Lidal et al., 2020; Mu et al., 2019; Warnink-Kavelaars et al., 2021; Warnink-Kavelaars, Beelen, Dekker, et al., 2019; Warnink-Kavelaars, Beelen, Goedhart, et al., 2019; Warnink-Kavelaars, van Oers, et al., 2021). Such problems, in turn, have been found to evoke behavioral and emotional problems in children with chronic illnesses (Glazebrook et al., 2003; Pinquart & Shen, 2011). Until now, it is largely unknown whether children and adolescents with HCTD suffer from decreased Health-Related Quality of Life (HRQoL) and mental health. The World Health Organization (WHO) has defined HRQoL and mental health as an integral part of functioning and health. HRQoL is defined as the perceived (subjective) health-related physical, mental, and social functioning of children and adolescents. Mental health is defined as a state of well-being in which children and adolescents realize their own abilities, can cope with the normal stresses of life, can study/work productively, and are able to make a contribution to community (World Health Organization, 2007).

There are few studies on HRQoL of children with HCTD. In a review on psychosocial outcomes of MFS (Nielsen et al., 2019), self-reported HRQoL was decreased in two studies (Handisides et al., 2019; Johansen et al., 2013) and unimpaired in another study (Mueller et al., 2016). HRQoL was also decreased in children with EDS (Johansen et al., 2013), hEDS (Malfait et al., 2017), and Hypermobile Spectrum Disorder (HSD) (Malfait et al., 2017), the current label for patients with joint hypermobility and musculoskeletal problems who do not meet the 2017 international clinical criteria for hEDS (Mu et al., 2019; Pacey et al., 2015). To the best of our knowledge, data on HRQoL of children with LDS are lacking.

Adults with MFS, LDS, and EDS reported that their physical condition and cardiovascular problems had a negative impact on quality of life (Nielsen et al., 2019; Velvin et al., 2019). Moreover, adults with hEDS and HSD reported decreased physical and psychosocial HRQoL (Berglund et al., 2015; Bovet et al., 2016; Johannessen et al., 2016; Rombaut et al., 2010; Scheper et al., 2016; Zeitoun et al., 2013).

The empirical literature on mental health of children with HCTD is limited. An older study reported attention deficit disorder with or without hyperactivity in 17% of children with MFS (Hofman et al., 1988). In addition, children with hEDS and HSD reported psychiatric disorders, most commonly anxiety and depression, in 41.3% (Mu et al., 2019). To the best of our knowledge, no studies have been published on mental health of children with LDS and EDS.

A review on adults with MFS reported co-occurrence of MFS and psychiatric disorders, but firm conclusions were not drawn (Gritti et al., 2015). Furthermore, adults with EDS, hEDS, and HSD reported an increased risk of psychiatric disorders (Baeza-Velasco et al., 2011; Berglund et al., 2015; Bulbena et al., 2017; Castori et al., 2010; Cederlöf et al., 2016; Hershenfeld et al., 2016; Lumley et al., 1994; Rombaut et al., 2011; Sinibaldi et al., 2015; Wasim et al., 2019).

This study aims to assess HRQoL and mental health of children and adolescents with HCTD using standardized validated questionnaires. To this end, we compared a large group of children and adolescents with HCTD to representative general population samples. In addition, we compared HRQoL and mental health of subgroups of children and adolescents with MFS and hEDS to representative general population samples.

2 | MATERIALS AND METHODS

2.1 | Study design

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

2.2 | Study population

Children and adolescents, aged 4–18, with MFS, LDS, EDS, and hEDS, were eligible for inclusion. Children and parents were recruited at the Expert Centers for MFS 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. Children and parents received written information on the study from their treating physician. To maximize representativeness of the HCTD sample, children were also recruited through the MFS and EDS patient associations in The Netherlands that announced the study on their websites. Interested parents contacted the research team by email or phone. Inclusion took place between February 2019 and January 2021. All parents of children 4–16 years and children themselves 12–18 years provided informed consent before they completed the online survey. To meet privacy regulations, the survey was anonymous. Therefore, we were not allowed to check the medical files on the parent-reported diagnosis of the child. Survey data were automatically imported into the Castor database. The Medical Ethics Review Committee of Amsterdam UMC (W18_346) and the Ethical Committee of Ghent University Hospital (EC2019/1958) approved the study protocol.

2.3 | Measures

2.3.1 | Sociodemographic characteristics

A custom-made parent-reported questionnaire collected information on the child's sex, age, HCTD diagnosis, and the sex and age of the parent who completed the survey.

2.3.2 | Parent-reported child HRQoL

Parent-reported Child HRQoL and parental and family impact were assessed with the parent-reported CHQ-PF50 (Landgraf et al., 1999; Wulffraat et al., 2001). The parent-reported CHQ-PF50 is normed for ages 5–18 and comprises Physical and Psychosocial sum scales and 12 subscales (Table 1). Of these 12 subscales, 8 scales investigate the child's HRQoL. To better understand the meaning and interpretation of sum and subscale scores as reported by parent-proxy, the CHQ-PF50 contains two subscales on the impact on parental time and distress and two subscales on family activities and cohesion (Landgraf et al., 1999; Wulffraat et al., 2001).

2.3.3 | Child-reported child HRQoL

Child-reported Child HRQoL and family impact were assessed with the CHQ-CF45 which is normed for ages 8–18 and contains 10 scales. Of these 10 scales, 8 scales investigate the child's HRQoL and 2 scales investigate family activities and cohesion. The CHQ-CF45 does not include sum and subscales (Landgraf et al., 1999; Landgraf et al., 2018; Raat et al., 2002).

For both CHQ questionnaires, a 4-week recall period applies for all scales except the Change of Health item, which pertains to the previous year. On both questionnaires, lower scores reflect decreased HRQoL. The CHQ-PF50 and CHQ-CP45 are widely used rating scales with well-studied and excellent psychometric properties (Landgraf et al., 1999; Landgraf et al., 2018; Raat et al., 2002; Wulffraat et al., 2001). Psychometric properties have also been established for the Dutch version (Raat et al., 2002; Wulffraat et al., 2001).

2.3.4 | Mental health

Mental health was assessed with the parent-reported Strengths and Difficulties Questionnaire (SDQ; Goodman & Goodman, 2009; Goodman, 2001; Maurice-Stam et al., 2018; van Widenfelt et al., 2003). The SDQ is normed for ages 2–18 and yields a total sum score (Total difficulties), two sum scores (Internalizing and Externalizing), and five subscale scores (Emotional symptoms, Conduct problems, Hyperactivity-Inattention, Peer problems, and Prosocial behavior). The Total difficulties total sum scale includes items of all subscales except the items of the Prosocial behavior subscale. The Internalizing sum scale contains all items of two subscales: Emotional problems and Peer problems, whereas the Externalizing sum scale contains all items of two subscales: Conduct problems and Hyperactivity-Inattention. Higher scores reflect decreased mental health, except for the Prosocial behavior subscale on which higher scores reflect well-developed prosocial behavior. Scores >90th percentile (Prosocial behavior <10th percentile) are defined as clinical scores (Goodman, 2001; Maurice-Stam et al., 2018). The SDQ is a widely used rating scale with well-studied and excellent psychometric properties (Goodman, 2001). Psychometric properties have also been established for the Dutch version (Maurice-Stam et al., 2018).

TABLE 1 Sex and age of the children of the total HCTD-group and subgroups

Child/adolescent	HCTD	MFS	LDS	EDS	hEDS
n (%)	126 (100)	74 (59)	8 (6)	15 (12)	29 (23)
Sex, *n* (%), female	51 (41)	22 (30)	5 (63)	7 (47)	17 (59)
Age (years), *M* (SD)	10.5 (4.0)	10.4 (4.1)	11.0 (3.6)	12.1 (4.3)	10.0 (3.7)

Abbreviations: EDS, Ehlers–Danlos syndromes; HCTD, heritable connective tissue disorders; hEDS, hypermobile Ehlers–Danlos syndrome; LDS, Loeys–Dietz syndrome; *M*, mean; MFS, Marfan syndrome; *n*, number; SD, standard deviation.

2.4 | Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS) version 26.0. The group sizes of the EDS-subgroup ($n = 15$) and LDS-subgroup ($n = 7$) were small, and analyses reported on these subgroups served explorative purposes only. The percentage of missing items was ≤ 4.8% on the parent-reported CHQ-PF50; ≤ 11.2% on the child-reported CHQ-CH45 and ≤ 5.1% on the parent-reported SDQ. Missing data were missing at random and were not related to sex or age. Multivariate Imputation by Chained Equations and Predictive Mean Matching was used to impute missing data (Eekhout et al., 2014).

The scores of the CHQ-PF50, CHQ-CF45, and SDQ 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. More specifically, the CHQ-PF50 data of our sample were compared with a representative U.S. population sample of 391 children, aged 11.5 (SD 3.7) years (Landgraf et al., 1999), the CHQ-CF45 data to a representative U.S. population sample of 1438 children, aged 12.5 (SD 3.1) years (Landgraf et al., 1999), and the SDQ data to a representative Dutch general population sample of 980 children, aged 10.7 (SD 4.5) years (Maurice-Stam et al., 2018). The CHQ-PF50 is normed for ages 5–18. Consequently, parent-reported CHQ-PF50 data of nine 4-year-old children were omitted from the analyses. The sample characteristics age and sex of the HCTD-group and the MFS- and hEDS-subgroups were compared with the representative samples using Chi-square tests and *t*-tests, respectively.

Subsequent analyses involved two steps. First, sum scores and subscale scores derived from the three questionnaires of the HCTD-group were compared with the appropriate representative samples, using *t*-tests, whereas the percentage of children obtaining clinical scores on the SDQ was compared using Chi-square tests. The age and sex of the HCTD-group did not differ from the age and sex distribution of the representative sample for any of the three questionnaires. In the second analysis step, the analyses of the HCTD-group were repeated for the MFS- and hEDS-subgroups. The age distribution of the subgroups did not differ from the representative samples. However, the sex distribution of the MFS-subgroup differed from the sex distribution of the representative sample for the CHQ-PF50 (Landgraf et al., 1999) ($p = 0.007$), CHQ-CF45 (Landgraf et al., 1999; $p = 0.004$) and the SDQ (Maurice-Stam et al., 2018; $p = 0.007$). Therefore, the analyses of the MFS-subgroup were performed for males and females separately.

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 (Field, 2018). 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 CHQ and SDQ, a *p*-value of ≤ 0.05 was considered statistically significant. To control for multiple testing, the analysis of the subscale scores used a *p*-value of ≤ 0.001 to determine statistical significance.

3 | RESULTS

3.1 | Study population

A total of 172 children, adolescents, and their parents agreed to participate. Forty-six participants did not start the validated questionnaires, leaving 126 children and adolescents with HCTD for the analyses. 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 ($n = 11$), Vascular EDS ($n = 1$), Dermatosparaxis EDS ($n = 1$), Arthrochalasia EDS ($n = 1$), and Classical like EDS ($n = 1$). Of all parents who completed the survey, 82% was female, and the mean (SD) age was 42.8 (7.0) years.

3.2 | Child HRQoL

3.2.1 | Parent-reported child HRQoL of the HCTD-group

Table 2 shows HRQoL assessed with parent-reported CHQ-PF50 and child-reported CHQ-CF45 of the HCTD-group, subgroups, and the U.S. representative general population sample.

Compared with the U.S. sample scores, the HCTD-group obtained significantly lower Physical and Psychosocial sum scores, translating into large and small effects, respectively. These results indicate that, according to parents, both physical and psychosocial problems lead to decreased HRQoL of children with HCTD. Further analyses on the subscales showed that physical and psychosocial problems could be traced back to significantly lower scores on subscales: Physical Functioning, Role/Social–Emotional/Behavioral, Role/Social–Physical, Bodily Pain, Mental Health, Self-Esteem, and General Health Perceptions translating into small- to large-sized effects (Table 2). These findings indicate decreased HRQoL of children with HCTD, manifesting in increased pain, decreased physical functioning and general health, low self-esteem, a negative mental health state and limitations in school-related and leisure activities, and participation with friends and family (Table 2).

3.2.2 | Parent-reported change in health over the last year of the HCTD-group

On the item "Change in Health over the last year", 15% of parents of the HCTD-group reported their children to have "somewhat better to much better" health, 69% reported health to be "about the same", and 16% reported "somewhat worse to much worse" health.

3.2.3 | Parent-reported parental and family impact of the HCTD-group

Further analyses on parental and family impact showed significantly lower scores on subscales Parental Impact-Emotional and Family

TABLE 2 HRQoL assessed with parent-reported CHQ-PF50 and child-reported CHQ-CF45 of the HCTD-group, subgroups, and the U.S. representative general population sample

CHQ-PF50	HCTD ($n = 117$)	U.S. norm ($n = 391$)	HCTD vs. norm *p*-value	Effect size Cohen's *d*	MFS ($n = 68$)	LDS ($n = 8$)	EDS ($n = 14$)	hEDS ($n = 27$)
Scales M (SD); range								
Sum scales								
Physical	41.2 (15.6); 0–60	53.0 (8.8); 5–64	*<0.001*	0.9	47.6 (11.1); 13–60	41.0 (9.8); 29–55	41.4 (18.9); 0–58	25.0 (13.8); 0–45
Psychosocial	49.1 (8.8); 21–64	51.2 (9.1); 6–64	*0.024*	0.2	50.4 (8.0); 21–64	53.5 (5.9); 43–61	48.4 (10.3); 27–63	45.1 (9.2): 30–58
Subscales								
Physical functioning	76.6 (28.4); 0–100	96.1 (13.9); 0–100	*<0.001*	0.9	85.9 (18.8); 17–100	82.6 (12.0); 67–100	78.1 (27.9); 22–100	50.4 (26.1); 0–89
Role/social–emotional/ behavioral	82.9 (28.4); 0–100	92.5 (18.6); 0–100	*<0.001*	0.4	90.3 (20.6); 22–100	98.6 (3.9); 89–100	84.1 (28.1); 11–100	58.8 (36.0); 0–100
Role/social–physical	78.3 (30.8); 0–100	93.6 (18.6); 8–100	*<0.001*	0.6	89.8 (23.1); 0–100	75.0 (21.8); 50–100	81.0 (38.6); 0–100	48.8 (28.1); 0–100
Bodily pain	62.7 (27.7); 0–100	81.7 (19.0); 0–100	*<0.001*	0.8	74.9 (23.3); 0–100	61.3 (27.0); 10–100	53.6 (25.3); 10–80	37.4 (21.7); 0–80
Behavior	75.2 (15.5); 30–100	75.6 (16.7); 0–100	*0.81*		77.1 (15.0); 43–100	77.0 (10.6); 60–96	75.7 (17.5); 43–100	69.8 (16.6); 30–92
Mental health	71.9 (13.3); 40–100	78.5 (13.2); 0–100	*<0.001*	0.5	75.1 (12.4); 45–100	76.3 (9.5); 60–90	69.3 (12.9); 45–90	63.9 (13.4); 40–85
Self-esteem	71.4 (13.9); 25–100	79.8 (17.5); 0–100	*<0.001*	0.5	73.4 (14.0); 25–100	75.0 (15.6); 54–100	71.7 (14.4); 33–96	65.3 (11.6); 38–79
General health perceptions	57.1 (19.7); 4–96	73.0 (17.3); 8–100	*<0.001*	0.8	61.9 (16.2); 18–96	53.2 (26.1); 9–77	61.6 (24.7); 4–89	43.9 (17.7); 9–71
Parental impact-emotional	70.9 (21.8); 0–100	80.3 (19.1); 0–100	*<0.001*	0.4	73.9 (20.6); 8–100	75.0 (18.4); 50–100	70.8 (29.2); 0–100	62.2 (20.3); 25–100
Parental impact-time	82.8 (25.6); 0–100	87.8 (19.9); 0–100	*0.023*		87.5 (20.8); 0–100	91.7 (9.8); 78–100	77.8 (38.0; 0–100	70.8 (28.4); 11–100
Family activities	79.8 (21.9); 17–100	89.7 (18.6); 0–100	*<0.001*	0.4	87.1 (16.6); 29–100	87.5 (12.6); 67–100	77.3 (26.4); 21–100	60.7 (23.2); 17–100
Family cohesion	72.6 (20.2); 0–100	72.3 (21.6); 0–100	*0.89*		71.0 (23.1); 0–100	75.6 (12.9); 60–85	71.1 (16.1); 60–100	76.5 (15.3); 60–100
CHQ-CF45	**HCTD ($n = 89$)**	**U.S. norm ($n = 1438$)**	**HCTD vs. norm *p*-value**	**Effect size Cohen's *d***	**MFS ($n = 51$)**	**LDS ($n = 6$)**	**EDS ($n = 12$)**	**hEDS ($n = 20$)**
Scales, *M* (SD); range								
Physical functioning	77.0 (23.3); 0–100	94.5 (12.6), 0–100	*<0.001*	0.9	83.9 (19.0); 17–100	77.8 (18.9); 50–100	77.7 (23.7); 33–100	58.7 (26.2); 0–93
Role/social–emotional/ behavioral	83.8 (22.7); 0–100	92.4 (16.5); 0–100	*<0.001*	0.4	86.6 (21.4); 0–100	88.9 (17.2); 67–100	84.7 (24.1); 33–100	74.5 (23.5); 17–100
Role social–physical	82.1 (27.1); 0–100	96.4 (13.7); 0–100	*<0.001*	0.7	91.3 (19.6); 0–100	86.1 (12.5); 67–100	83.3 (31.0); 0–100	56.7 (31.3); 0–100
Bodily pain	58.7 (27.8); 0–100	83.4 (19.6); 0–100	*<0.001*	1.0	70.3 (22.1); 0–100	48.3 (22.3); 10–70	53.3 (26.4); 0–80	35.2 (27.7); 0–80
Behavior	72.6 (14.9); 29–100	71.9 (18.7); 0–100	*0.73*		75.6 (14.3); 29–100	72.6 (12.6); 62–96	67.6 (17.8); 33–91	68.6 (14.1); 46–89
Mental health	64.1 (10.5); 31–94	77.9 (14.6); 11–100	*<0.001*	1.1	64.5 (9.0); 42–83	67.6 (11.2); 53–86	60.1 (12.6); 33–72	64.3 (12.7); 31–94
Self-esteem	78.0 (12.3); 43–100	81.7 (18.7); 0–100	*0.07*		79.7 (11.5); 57–100	79.1 (10.5); 64–93	77.7 (14.8); 50–100	73.7 (12.7); 43–93
General health perceptions	61.1 (25.1); 0–100	79.5 (16.6; 5–100	*<0.001*	0.8	67.8 (21.9); 22–100	51.3 (36.4); 6–100	60.3 (24.9); 6–100	47.4 (23.9); 0–97
Family activities	84.4 (21.3); 8–100	85.4 (21.5); 0–100	*0.17*		90.7 (14.4); 42–100	90.3 (17.0); 58–100	77.1 (25.4); 25–100	71.0 (27.1); 8–100
Family cohesion	77.3 (20.1); 0–100	75.4 (22.6); 0–100	*0.44*		80.5 (16.2); 46–100	79.1 (15.9); 60–100	68.8 (30.5); 0–100	73.7 (22.3); 30–100

Note: Lower scores reflect decreased HRQoL.

Abbreviations: CHQ-PF50, Child Health Questionnaire-Parent form; CHQ-CF45, Child Health Questionnaire-Child form; *d*, Cohen's *d* effect size; EDS, Ehlers–Danlos syndromes; HCTD, heritable connective tissue disorders; hEDS, hypermobile Ehlers–Danlos syndrome; LDS, Loeys–Dietz syndrome; *M*, mean; MFS, Marfan syndrome; *n*, number; *p*, probability; SD, standard deviation.

Activities compared with the U.S. sample scores, whereas subscales Parental Impact-Time and Family Cohesion showed no significant differences. This indicates that parents of children with HCTD experience a significantly increased amount of distress and limited family activities (Table 2).

3.2.4 | Parent-reported child HRQoL of the male and female MFS- and hEDS-subgroups

Table 3 shows HRQoL assessed with parent-reported CHQ-PF50 and child-reported CHQ-CF45 of the male and female MFS-subgroups, and the male and female U.S. representative general population samples.

On the CHQ-PF50, both, males and females with MFS obtained significantly lower Physical sum scores compared with the scores of the U.S. samples. No differences were found for the Psychosocial sum scores. Further analyses showed significantly lower scores on subscales Physical Functioning and General Health Perceptions. These findings indicate decreased physical HRQoL of children (male and female) with MFS, which manifest in decreased physical functioning and general health.

The hEDS-subgroup obtained significantly lower Physical ($p < 0.001$, $d = 2.2$) and Psychosocial ($p = 0.001$, $d = 0.4$) sum scores compared with the scores of the U.S. sample. These results were explained by significantly lower scores on the subscales Physical Functioning ($p < 0.001$, $d = 1.0$), Role/Social–Emotional/Behavior ($p < 0.001$, $d = 0.7$), Role/Social–Physical ($p < 0.001$, $d = 1.0$), Bodily Pain ($p < 0.001$, $d = 1.0$), Mental Health ($p < 0.001$, $d = 0.6$), Self-Esteem ($p < 0.001$, $d = 0.5$), and General Health Perceptions ($p < 0.001$, $d = 0.7$; Table 1). These findings indicate decreased physical and psychosocial HRQoL of children with hEDS, which manifests in increased pain, decreased physical functioning and general health, low self-esteem, a negative mental health state, and limitations in school-related and leisure activities, and participation with friends and family.

3.2.5 | Parent-reported change in health over the last year of the male and female MFS- and hEDS-subgroups

On the item "Change in Health over the last year", parents of the male and female MFS-subgroups and hEDS-subgroup, reported their children to have "somewhat better to much better" health in 11%, 1%, and 26%, respectively, "about the same" health in 80%, 74%, and 52%, respectively and "somewhat worse to much worse" health in 9%, 25%, and 22%, respectively.

3.2.6 | Parent-reported parental and family impact of the male and female MFS- and hEDS-subgroups

Compared with the U.S. sample scores, parents of children (male and female) with MFS did not experience a significantly different amount of distress whereas parents children with hEDS experienced an increased amount of distress ($p < 0.001$, $d = 0.4$) and limitations in their personal time ($p < 0.001$, $d = 0.4$). The impact on family was not significantly different of parents of the male and female MFS- and hEDS-subgroups compared with the U.S. sample. These findings indicate that parents of children with hEDS experience a significantly increased amount of distress and limited family activities whereas parents of children (male and female) with MFS do not (Tables 2 and 3).

3.2.7 | Child-reported child HRQoL of the HCTD-group

Compared with the scores of the U.S. sample, the HCTD-group obtained significantly lower scores on 6 of 10 scales: Physical Functioning, Role/Social–Emotional/Behavioral, Role/Social–Physical, Bodily Pain, Mental Health, and General Health Perceptions translating into small- to large-sized effects. Thus, children with HCTD report decreased HRQoL reflected in increased pain, decreased physical functioning and general health, a negative mental health state, limitations in school-related and leisure activities, and participation with friends and family (Table 1).

3.2.8 | Child-reported change in health over the last year of the HCTD-group

On the item "Change in Health over the last year", 18% of the HCTD-group self-reported to have "somewhat better to much better" health, 60% reported health to be "about the same" health, and 22% reported "somewhat worse to much worse" health.

3.2.9 | Child-reported child HRQoL of the male and female MFS- and hEDS-subgroups

The male and female MFS-subgroups obtained significantly lower scale scores on Physical Functioning, Mental Health, and General Health compared with the scores of the U.S. sample. In addition, the female MFS-subgroup obtained a significantly lower scale score on Bodily Pain (Table 3).These findings indicate that children (male and female) with MFS report decreased HRQoL as indicated by increased pain, decreased physical functioning and general health, and a negative mental health state.

The hEDS-subgroup obtained significantly lower scale scores on Physical Functioning ($p < 0.001$, $d = 1.7$), Role/Social–Emotional/Behavior ($p < 0.001$, $d = 0.8$), Role/Social–Physical ($p < 0.001$, $d = 1.6$), Bodily Pain ($p < 0.001$, $d = 2.0$), Mental Health ($p < 0.001$, $d = 1.0$), Self-Esteem ($p < 0.001$, $d = 0.4$), General Health Perceptions ($p < 0.001$, $d = 1.6$), and Family Activities ($p < 0.001$, $d = 0.6$) compared with the scores of the U.S. sample (Table 1). Thus, children with hEDS report decreased HRQoL as reflected in increased pain, decreased physical functioning and general health, low self-esteem, a negative mental health state and limitations in school-related and leisure activities, and participation with friends and family.

TABLE 3 HRQoL assessed with parent-reported CHQ-PF50 and child-reported CHQ-CF45 of the male and female MFS-subgroups, and the male and female U.S. representative general population samples

CHQ-PF50	MFS male ($n = 52$)	U.S. norm male ($n = 212$)	MFS male vs. norm *p*-value	Effect size Cohen's *d*	MFS female ($n = 22$)	U.S. norm female ($n = 177$)	MFS female vs. norm *p*-value	Effect size Cohen's *d*
Scales M (SD); range								
Sum scales								
Physical	48.1 (10.8); 11–60	52.4 (10.3); 0.5–64	*0.01*	0.4	46.4 (10.7); 17–60	54.9 (6.0); 28–65	*<0.001*	1.0
Psychosocial	50.5 (7.4); 28–63	50.7 (4.9); 16–64	*0.81*		50.6 (9.2); 22–64	51.9 (8.7); 7–65	*0.51*	
Subscales								
Physical functioning	85.9 (18.5); 22–100	94.9 (17.0); 0–100	*<0.001*	0.5	83.6 (19.1); 17–100	97.9 (6.9); 61–100	*<0.001*	1.0
Role/social–emotional/ behavioral	91.0 (20.0); 22–100	91.4 (20.8); 0–100	*0.83*		88.8 (21.1); 33–100	93.9 (15.6); 0–100	*0.17*	
Role/social–physical	90.9 (21.0); 0–100	92.5 (23.3); 0–100	*0.65*		85.3 (19.2); 17–100	95.1 (14.7); 0–100	*0.01*	
Bodily pain	77.2 (20.4); 10–100	82.8 (19.2); 19–100	*0.06*		69.6 (23.9); 0–100	80.3 (18.9); 0–100	*0.02*	
Behavior	77.3 (14.9); 43–100	74.1 (16.3); 25–100	*0.20*		76.7 (14.9); 47–100	77.5 (17.0); 0–100	*0.75*	
Mental health	75.6 (12.2); 50–100	79.6 (13.2); 20–100	*0.05*		73.8 (12.5); 45–90	77.1 (13.2); 20–100	*0.27*	
Self-esteem	73.5 (12.7); 38–100	79.6 (17.7); 0–100	*0.02*		73.1 (17.0); 25–100	79.9 (17.4); 25–100	*0.09*	
General health perceptions	61.1 (16.5); 18–96	71.6 (18.1); 8–100	*<0.001*	0.6	63.8 (15.2); 27–96	74.7 (16.3); 23–100	*<0.001*	0.8
Parental impact-emotional	71.8 (20.3); 8–100	78.0 (20.6); 0–100	*0.05*		79.1 (21.0); 8–100	82.9 (16.9); 21–100	*0.18*	
Parental impact-time	88.6 (15.1); 44–100	85.8 (21.5); 0–100	*0.38*		85.2 (30.1); 0–100	90.7 (16.4); 11–100	*0.19*	
Family activities	86.5 (15.2); 42–100	88.9 (20.5); 0–100	*0.45*		88.4 (19.1); 29–100	91.0 (15.7); 20–100	*0.48*	
Family cohesion	69.5 (22.8); 0–100	73.4 (21.2); 0–100	*0.24*		74.3 (23.3); 0–100	70.9 (22.2); 0–100	*0.48*	
CHQ-CF45	**MFS male ($n = 35$)**	**U.S. norm male ($n = 718$)**	**MFS male vs. norm *p*-value**	**Effect size Cohen's *d***	**MFS female ($n = 16$)**	**U.S. norm female ($n = 720$)**	**MFS female vs. norm *p*-value**	**Effect size Cohen's *d***
Scales M (SD); range								
Physical functioning	85.6 (18.1); 19–100	94.5 (12.8); 0–100	*<0.001*	0.6	79.9 (20.9); 17–100	94.5 (12.4); 0–100	*<0.001*	0.9
Role/social–emotional/ behavioral	87.3 (19.4); 22–100	92.1 (17.1); 0–100	*0.11*		85.2 (26.2); 0–100	92.7 (15.9); 0–100	*0.07*	
Role/social–physical	92.6 (14.3); 40–100	96.3 (14.0); 0–100	*0.13*		88.7 (26.0); 0–100	96.4 (13.4); 0–100	*0.03*	
Bodily pain	77.9 (20.4); 21–100	84.3 (18.9); 0–100	*0.04*		64.7 (25.7); 0–100	82.5 (20.3); 0–100	*<0.001*	0.8
Behavior	74.6 (15.3); 29–100	70.6 (19.4); 4–100	*0.23*		76.8 (11.3); 58–96	73.1 (17.9); 0–100	*0.41*	
Mental health	65.8 (8.5); 42–79	79.0 (13.3); 11–100	*<0.001*	1.2	61.4 (9.2); 47–83	76.9 (15.8); 17–100	*<0.001*	1.2
Self-esteem	79.7 (11.0); 48–100	81.3 (19.0); 0–100	*0.62*		79.6 (12.8); 57–96	82.0 (18.4); 7–100	*0.60*	
General health perceptions	70.0 (19.9); 27–100	79.6 (16.7); 5–100	*<0.001*	0.5	58.1 (22.8); 22–100	79.4 (16.5); 25–100	*<0.001*	1.1
Family activities	90.7 (13.1); 36–100	85.5 (21.9); 0–100	*0.16*		91.1 (15.2); 42–100	85.3 (21.1); 0–100	*0.28*	
Family cohesion	80.0 (17.2); 35–100	75.3 (22.7); 0–100	*0.23*		81.9 (14.6); 27–100	75.5 (22.4); 0–100	*0.26*	

Note: Lower scores reflect decreased HRQoL.

Abbreviations: CHQ-PF-50, Child Health Questionnaire-Parent form; CHQ-CF45, Child Health Questionnaire-Child form; *d*, Cohen's *d* effect size; *M*, mean; MFS, Marfan syndrome; *n*, number; *p*, probability; SD, standard deviation.

3.2.10 | Child-reported change in health over the last year of the male and female MFS- and hEDS-subgroups

On the item "Change in Health over the last year", the male and female MFS-subgroups and hEDS-subgroup self-reported "somewhat better to much better" health in 14%, 6%, and 44%, respectively, "about the same" health in 76%, 74%, and 37%, respectively, and "somewhat worse to much worse" health in 10%, 20%, and 19%, respectively.

3.3 | Mental health

3.3.1 | Parent-reported mental health of the HCTD-group

Table 4 shows mental health assessed with the parent-reported SDQ of the HCTD-group, subgroups, and the Dutch representative general population sample.

Compared with the Dutch sample scores, the HCTD-group obtained significantly higher scores on the Total difficulties sum scale, with this group difference translating into a small-sized effect. This finding indicates that parents of children with HCTD reported that their children demonstrate decreased mental health.

To further study the nature of this finding, scores on the Internalizing and Externalizing sum scales and the five subscales of the HCTD-group were compared with the representative population samples. Results showed that the HCTD-group obtained significantly higher scores on the Internalizing sum scale, translating into a small-sized effect. No group differences were found on the Externalizing sum scale. In addition, the HCTD-group obtained significantly higher scores in the Emotional symptoms subscale translating into a medium-sized effect. None of the other subscale scores showed significant group differences. Taken together, the findings indicate decreased mental health of children with HCTD, which manifests in internalizing and emotional symptoms.

The percentage of children of the HCTD-group with parent-reported scores above the clinical cutoff on the Total difficulties sum scale was significantly higher than the Dutch sample (9.5% vs. 19.2%, $p = 0.001$). Furthermore, a significantly higher percentage of children of the HCTD-group obtained scores above the clinical cutoff on the Internalizing sum scale (9.3% vs. 16.7%, $p = 0.011$) and the subscales Emotional symptoms (9.1% vs. 23.3%, $p < 0.001$), Hyperactivity-Inattention (12.1% vs. 20.8%, $p = 0.008$), and Prosocial behavior (10.3% vs. 22.5%, $p < 0.001$). Thus, compared with a Dutch sample, a higher percentage of children with HCTD show clinical levels of mental health problems, manifesting in higher rates of clinical scores of internalizing symptoms, emotional symptoms, and hyperactivity-inattention problems. In addition, the HTCD-group showed well-developed prosocial behavior.

3.3.2 | Parent-reported mental health of the male and female MFS- and hEDS-subgroups

The male and female MFS-subgroups showed no significant differences compared with the Dutch sample, on any of the SDQ sum and subscales. Thus, according to parent-reports, no evidence was found for compromised mental health of children (male and female) with MFS. The percentage of children of the male and female MFS-subgroups with scores above the clinical cutoff was only significantly higher on the Prosocial behavior subscale compared with the Dutch sample (14.1% vs. %, 29.8, $p < 0.001$; 6.2% vs. 14.7%, $p < 0.001$, respectively).

The hEDS-subgroup obtained significantly higher scores on the Total difficulties sum scale compared with the representative general population sample, with this group difference translating into a small-sized effect ($p < 0.001$, $d = 0.3$). This finding indicates that parents of children with hEDS reported their children to show decreased mental health. Further analysis showed that the hEDS-subgroup obtained significantly higher scores on the Internalizing sum scale, translating into a large-sized effect ($p < 0.001$, $d = 0.9$) but no group differences were found on the Externalizing sum scale. The hEDS-subgroup obtained higher scores on the subscales Emotional symptoms ($p < 0.001$, $d = 1.3$), and Hyperactivity-Inattention ($p = 0.039$, $d = 0.4$), translating into a large- and small-sized effect, respectively. Taken together, these findings indicate decreased parent-reported mental health of children with hEDS, which manifests in internalizing symptoms, emotional symptoms, and hyperactivity-inattention problems. Compared with the Dutch sample, the percentage of children of the hEDS-subgroup with scores above the clinical cutoff was significantly higher on the Total difficulties sum scale (9.5% vs. 30.8%, $p < 0.001$); the Internalizing sum scale (9.3% vs. 30.8%, $p < 0.001$); and the subscales Emotional symptoms (9.1% vs. 42.3%, $p < 0.001$) and Hyperactivity-Inattention (12.1% vs. 30.8%, $p = 0.005$). Taken together, these findings indicate that a higher percentage of children with hEDS show clinical levels of mental health problems, which manifests in higher rates of clinical scores of internalizing symptoms, emotional symptoms, and hyperactivity-inattention problems.

4 | DISCUSSION

This is the first study into HRQoL and mental health of children and adolescents with HCTD using standardized validated questionnaires CHQ and SDQ. We find decreased HRQoL and mental health of children and adolescents with HCTD compared with representative general population samples, with most adverse outcomes in children with hEDS and least in those with MFS. In addition, parents of children and

TABLE 4 Mental health assessed with the parent-reported SDQ of the HCTD-group, subgroups and the U.S. representative general population sample

Scales, *M* (SD); range	HCTD Cronbach's alpha	HCTD ($n = 126$)	Dutch norm Cronbach's alpha	Dutch norm ($n = 980$)	HCTD vs. norm *p*-value	Effect size Cohen's *d*	MFS ($n = 74$)	LDS ($n = 8$)	EDS ($n = 15$)	hEDS ($n = 29$)
Total difficulties (0–40)	0.83	9.1 (6.3); 0–25	0.84	7.6 (5.7); 0–33	*0.01*	0.3	8.3 (5.9); 0–24	6.4 (6.9); 0–22	9.5 (6.1); 1–20	12.0 (6.6); 3–25
Internalizing (0–20)	0.73	4.4 (3.4); 0–16	0.79	3.2 (3.2); 0–17	*<0.001*	0.4	3.7 (3.0); 0–14	3.5 (3.1); 0–10	4.7 (3.3); 0–15	6.5 (3.8); 2–16
Externalizing (0–20)	0.80	4.7 (4.0); 0–13	0.77	4.4 (3.5); 0–19	*0.34*		4.6 (4.0); 0–13	2.9 (4.1); 0–12	4.8 (3.5); 0–12	5.5 (4.0); 0–12
Emotional symptoms (0–10)	0.73	3.0 (2.4); 0–10	0.73	1.9 (2.0); 0–10	*<0.001*	0.5	2.3 (2.1); 0–8	2.1 (1.7); 0–5	3.5 (2.4); 0–10	4.8 (2.4); 1–9
Conduct problems (0–10)	0.42	–	0.54	1.2 (1.4); 0–10	–		–	–	–	–
Hyperactivity-inattention (0–10)	0.87	3.6 (3.3); 0–10	0.82	3.3 (2.7); 0–10	*0.24*		3.5 (3.2); 0–10	1.9 (3.4); 0–10	3.3 (2.6); 0–8	4.4 (3.5); 0–10
Peer problems (0–10)	0.61	1.4 (1.7); 0–8	0.66	1.3 (1.7); 0–10	*0.65*		1.4 (1.7); 0–7	1.4 (2.0); 0–5	1.1 (1.3); 0–4	1.7 (1.9); 0–8
Prosocial behavior (0–10)	0.74	8.1 (2.1); 1–9	0.72	8.1 (1.9); 0–10	*0.98*		7.9 (2.2); 1–10	8.6 (1.3); 6–10	8.1 (2.2); 3–10	8.6 (1.7); 4–10

Note: Scales with internal consistency Cronbach's alpha <0.50 were not analyzed and presented with "–." Higher scores reflect decreased mental health, with the exception of the Prosocial behavior scale on which higher scores reflect well-developed prosocial behavior.

Abbreviations: *d*, Cohen's *d* effect size; EDS, Ehlers–Danlos syndromes; HCTD, heritable connective tissue disorders; hEDS, hypermobile Ehlers–Danlos syndrome; LDS, Loeys–Dietz syndrome; *M*, mean; MFS, Marfan syndrome; *n*, number; *p*, probability; SD, standard deviation.

adolescents with HCTD experience a significantly increased amount of distress and limited family activities.

4.1 | Child HRQoL

Further study of the nature of the observed decreased HRQoL of the HCTD-group indicates that, according to parents, both physical and psychosocial problems contribute to decreased HRQoL. These problems manifest in increased pain, decreased physical functioning and general health, low self-esteem, a negative mental health state, limitations in school-related and leisure activities, and participation with friends and family. Children and adolescents themselves report similar findings but did not report experiencing low self-esteem and limitations in family activities. Our results are in line with the available studies on HRQoL of subgroups of children and adolescents with MFS (Handisides et al., 2019; Johansen et al., 2013), EDS (Johansen et al., 2013), hEDS and HSD (Castori et al., 2017; Mu et al., 2019; Pacey et al., 2015) and with studies on adults with HCTD (Berglund et al., 2015; Bovet et al., 2016; Johannessen et al., 2016; Nielsen et al., 2019; Rombaut et al., 2010; Scheper et al., 2016; Velvin et al., 2019; Zeitoun et al., 2013).

In subsequent analyses on parent-reported and child-reported HRQoL of the male and female MFS- and hEDS-subgroups, we find that children with hEDS report increased Physical and Psychosocial sum scores, whereas the male and female MFS-subgroups report only increased Physical sum scores. The hEDS-subgroup experiences low self-esteem, a negative mental health state, limitations in school-related and leisure activities, and participation with friends and family. In contrast, the male and female MFS-subgroups does not report these limitations. Our results are supported by the studies on children with hEDS and HSD who also reported decreased physical and psychosocial HRQoL (Mu et al., 2019; Pacey et al., 2015). In addition, two studies on children with MFS reported decreased physical and psychosocial HRQoL (Handisides et al., 2019; Johansen et al., 2013) and one study reported normal HRQoL (Mueller et al., 2016). These discrepant findings may be due to differences between studies of the questionnaires to assess HRQoL.

Interestingly, in our study, both parents of male and female MFS- and hEDS-subgroups reported on the CHQ-PF50 their children to have decreased physical functioning and general health. The results of the hEDS-subgroup translate into large effect sizes, whereas those of the male and female MFS-subgroups translate into moderate effect sizes. These effect sizes support the idea that the perceived severity of physical problems causes limitations in activities and participation, thus negatively affecting daily life functioning and health. In our study, parents of children with hEDS also report decreased psychosocial HRQoL. The reported low self-esteem and a negative mental health state may result in decreased satisfaction with appearance and abilities, and negatively affect social confidence. This may again limit activities and participation with friends and thereby further decrease psychosocial HRQoL.

Noteworthy, in our study, children (male and female) with MFS report increased pain and a negative mental health state, whereas their parents report no such problems. Because of the heritable nature of HCTD, parents and children of one family may be diagnosed with (the same) HCTD. Parental HCTD-related experiences of their own childhood may enable these parents to appreciate problems of their children (Warnink-Kavelaars, de Koning, et al., 2021; Warnink-Kavelaars, Beelen, Dekker, et al., 2019; Warnink-Kavelaars, Beelen, Goedhart, et al., 2019; Warnink-Kavelaars, van Oers, et al., 2021). It is of additional value to include the perspectives of both parents and children.

4.2 | Change in health

In our study, parents and children with HCTD, MFS (male and female), and hEDS report in around one of the five cases "somewhat worse to worse" change in health over the last year. These results may be explained by the developing physical features, such as pain of children with HCTD (Castori et al., 2017; Loeys et al., 2010; Loeys & Dietz, 1993; MacCarrick et al., 2014; Malfait et al., 2017; Meester et al., 2017; Van Laer et al., 2014; Warnink-Kavelaars, de Koning, et al., 2021; Warnink-Kavelaars, van Oers, et al., 2021). Other studies also reported increased pain of children with HCTD, which negatively influenced activities and participation in daily life (Mu et al., 2019; van Meulenbroek, Conijn, et al., 2020; van Meulenbroek, Huijnen, et al., 2020; Warnink-Kavelaars et al., 2021; Warnink-Kavelaars, van Oers, et al., 2021). These experienced limitations in activities and participation may be one of the critical factors in decreased HRQoL. Given the profound impact of decreased HRQoL on functioning and health, we recommend clinicians to systemically evaluate HRQoL by standardized validated questionnaires.

4.3 | Parental and family impact

Parents of children with HCTD experience a significantly increased amount of distress and limited family activities compared with the U.S. sample. Subsequent analyses show that, compared with the U.S. representative sample, parents of children with hEDS experience an increased amount of distress and limitations in their personal time whereas parents of children (male and female) with MFS experience a comparable amount of distress. Our previous study also showed comparable distress in parents of children with MFS compared with a representative general population (Warnink-Kavelaars, de Koning, et al., 2021, Warnink-Kavelaars, van Oers, et al., 2021). On the other hand, in our previous qualitative interview studies, parents experienced parental burden due to high care needs of their child with MFS, concerns about the child's physical and psychosocial development, lack of support, and limited social life (Warnink-Kavelaars, Beelen, Dekker, et al., 2019; Warnink-Kavelaars, Beelen, Goedhart, et al., 2019). To the best of our knowledge, there are no studies on

distress in parents of children with hEDS. The International Classification of Functioning and Health, developed by the WHO, recognizes parents and family as important pervasive aspects of child functioning and health (World Health Organization, 2007). Therefore medical professionals should be aware of the parental and family impact.

4.4 | Mental health

Further study of the nature of the observed decreased mental health of the HCTD-group indicates that, according to parents, decreased mental health manifests as internalizing and emotional symptoms. This is in line with a study on mental health of children with hEDS and HSD (Mu et al., 2019), an older study on children with MFS (Hofman et al., 1988) as well as with studies on adults with EDS, hEDS, and HSD (Baeza-Velasco et al., 2011; Berglund et al., 2015; Bulbena et al., 2017; Castori et al., 2010; Cederlöf et al., 2016; Hershenfeld et al., 2016; Lumley et al., 1994; Rombaut et al., 2011; Sinibaldi et al., 2015; Wasim et al., 2019). Moreover, studies on children with chronic illnesses with related physical impairments and limitations in daily life have shown that such chronic conditions may evoke behavioral and emotional problems (Glazebrook et al., 2003; Pinquart & Shen, 2011). As decreased mental health negatively influences daily life, we strongly recommend systemic monitoring mental health.

The subsequent analyses of the HCTD-subgroup on parent-reported mental health showed evidence for compromised mental health of children with hEDS. Also one study on children with hEDS and HSD (Mu et al., 2019) and studies on adults with EDS, hEDS, and HSD reported an increased risk of psychiatric disorders (Baeza-Velasco et al., 2011; Berglund et al., 2015; Bulbena et al., 2017; Castori et al., 2010; Cederlöf et al., 2016; Hershenfeld et al., 2016; Lumley et al., 1994; Rombaut et al., 2011; Sinibaldi et al., 2015; Wasim et al., 2019). Interestingly, children (male and female) with MFS showed no significant differences on the SDQ scores compared with the Dutch sample scores. This was not in line with a 30-year-old study on children with MFS which reported elevated rates of attention deficit disorder with or without hyperactivity (Hofman et al., 1988). However, a review on adults with MFS reported co-occurrence of MFS and psychiatric disorders, but firm conclusions were not drawn (Gritti et al., 2015). Moreover, in our study, the male and female MFS-subgroups were reported to have a clinically well-developed prosocial behavior. Again, the level of experienced physical problems and limitations in daily life may be the critical factor in mental health differences for the MFS- and hEDS-subgroups. Furthermore, prosocial behavior may act as a protector against decreased mental health.

4.5 | Strength and limitations

Our study is the first to study HRQoL and mental health in a large sample of children and adolescents with HCTD and subgroups compared representative general population samples on the CHQ and SDQ.

However, our study also has a few limitations. First, our CHQ data were compared with the data of a U.S. representative general population sample normed for ages 5–18. Therefore, we had to omit CHQ-PF50 data from nine parents of 4 -years- olds from the analyses. Second, there may be cultural differences between the Dutch-Flemish and U.S. population, which may have influenced our results. A review on child and adolescent psychopathology of 44 societies, showed that on the Child Behavior Check List the mean Total Problem sum scores for 26 societies (including The Netherlands, Belgium, and United States), fell within 1 SD of the overall mean. This indicates certain consistencies between The Netherlands, Belgium, and United States (Rescorla et al., 2012). 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 rediagnosed because they are not regularly treated in one of the expert centers. Fourth, our study did not comprise physical data that could be related to the experienced HRQoL and mental health. To determine factors that influence HRQoL and mental health of children with HCTD, our future research will therefore combine measurements of physical characteristics, fatigue, pain, muscle strength, physical fitness, activity monitoring, and validated questionnaires on each of the domains of the functioning and health.

5 | CONCLUSION

This study shows that children and adolescents with HCTD report decreased HRQoL and mental health, with most adverse outcomes reported in children with hEDS and least in those with MFS. In addition, their parents experience a significant increased amount of distress and limited family activities. These findings call for systematic monitoring of HRQoL and mental health of children and adolescents with HCTD and parental and family impact over time. Moreover, interdisciplinary tailored interventions should be developed to improve HRQoL and mental health of children with HCTD as well as parental and family support interventions.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Jessica Warnink-Kavelaars, Lisanne E. de Koning, Raoul H. H. Engelbert, Lies Rombaut, Annemieke I. Buizer, Leonie A. Menke, Mattijs W. Alsem, and Jaap Oosterlaan contributed to the study conception and design. The members of the Pediatric Heritable Connective Tissue Disorders Study Group delivered a substantial contribution to acquisition of data. Data collection and analyses were performed by Jessica Warnink-Kavelaars and Lisanne de Koning. The first draft of the article was written by Jessica Warnink-Kavelaars and all authors commented on previous versions of the article. All authors read and approved the final article.

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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